NOVEL PPAR AGONISTS, PHARMACEUTICAL COMPOSITIONS AND USES THEREOF

[0001] This application claims benefit under 35 U.S.C. § 119(e) of United States Provisional Application Serial Number. 60/455,375, filed on March 15, 2003, which is herein incorporated by reference in its entirety for all purposes.

1. Technical Field

[0002] This invention relates to the field of prevention and treatment of inflammatory and metabolic disorders, in particular, obesity and weight gain, and insulin resistance syndromes. More specifically, this invention relates to compounds that partially activate the PPARγ isoform and which may also inhibit the angiotensin II type 1 receptor (AT1).

2. Background

[0003] Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor superfamily of ligand-activated transcription factors. Three subtypes of PPARs have been isolated from mouse and human sources, *i.e.*, PPARα, PPARγ, and PPARδ (Willson *et al.*, *Annu Rev Biochem.* **2001**, 70:341-367). The PPARs are important regulators of intermediary (carbohydrate, lipid and protein) metabolism, energy metabolism, cell growth, cell differentiation, cell maturation, phenotype transition, apoptosis, neovascularization, angiogenesis, inflammation, immune regulation and the immune response. Compounds that activate PPARs are useful for the treatment and/or prevention of a variety of clinical disorders, including but not limited to, metabolic disorders, cardiovascular disorders, neurodegenerative disorders, autoimmune disorders, immunoregulatory disorders, metabolic syndrome, obesity, pre-diabetes, type 2 diabetes and other insulin resistant syndromes, hypertension, atherosclerosis, dyslipidemia, inflammatory skin diseases (*e.g.*, psoriasis) inflammatory bowel disease and inflammatory neurodegenerative diseases (*e.g.*, multiple sclerosis and Alzheimer's disease). (Pershadsingh, *Expert Opin Investig Drugs.* **1999**, 8:1859-1872; Debril *et al.*, *J Mol Med.* **2001**, 79:30-47; Delerive *et al.*, *J Endocrinol.* **2001**;169:453-9; Clark, *J Leukoc Biol.* **2002**, 71:388-400; Ellis *et al.*, *Arch Dermatol.* **2000**, 136:609-16; Lewis *et al. Am J Gastroenterol.* **2001**, 6:3323-8; Landreth *et al.*, *Neurobiol Aging.* **2001**, 22:937-44; Feinstein *et al.*, *Ann Neurol.* **2002**,

51:694-702). Metabolic syndrome includes the metabolic syndrome as defined by either the World Health Organization (WHO) or the National Cholesterol Education Program (NCEP) (Zimmet *et al.*, *Nature* **2001**, 414:782-7; Alberti *et al.*, *Diabet Med.* **1998**, 15:539-53).

[0004] Compounds which activate PPARs include, but are not limited to, thiazolidinediones (*e.g.*, rosiglitazone, pioglitazone, troglitazone, MK 767 (KRP-297), MCC-555, netoglitazone, balaglitazone, rivoglitazone, CLX-0921, R-483, NIP-221, NIP-223, DRF-2189), and the like that primarily activate PPARγ or PPARγ and PPARα, non-thiazolidinediones that can activate any combination of PPARγ, PPARα and PPARδ (*e.g.*, JTT-501, LSN862, DRF 4832, LM 4156, LY 510929, LY 519818, TY 51501, X 334, tesaglitazar, farglitazar, GW-7282, TAK-559, T-131, RG-12525, LY-510929, LY-519818, BMS-298585, DRF-2725, GW-1536, GI-262570, TZD18 (Merck), DRF-2655, and the like), certain tyrosine-based derivatives (*e.g.*, GW1929, GW7845), phenylacetic acid-based derivatives, phenoxazine phenyl propanoic acid derivatives (*e.g.*, DRF 2725, DRF 2189), cinammic and dihydrocinammic acid-based derivatives (*e.g.*, tesaglitazar (AZ 242)), and 3-phenyl-7-propylbenzisoxazoles (Adams *et al.*, *Bioorg Med Chem Lett.* **2003**, 13:931-5), that can activate PPARγ in combination with PPARα or PPARδ or both PPARα and PPARδ (also see Table 1, in: Miller AR, Etgen GJ. *Expert Opin Investig Drugs.* **2003,** 12:1489-500). Although some compounds primarily activate PPARα alone or PPARδ alone, more commonly such compounds also activate, to least some degree, PPARγ.

[0005] Compounds which antagonize the angiotensin II type 1 receptor and also activate PPARγ include, but are not limited to 2-methyl-2-[4-(2-[5-methyl-2-aryloxazol-4-yl]ethoxy)phenoxy]propionic acid PPARα/γ agonist derivatives (Brooks *et al.*, *J Med Chem* **2001**, 44:2061-4) N-(2-Benzoylphenyl)-L-tyrosine PPARγ agonists (Henke *et al.*, *J Med Chem* **1998,** 41:5020-36; dihydrocinnamate PPARα/γ agonist derivatives (Cronet *et al.*, *Structure* **2001**, 9:699-706. Another angiotensin II type 1 receptor blocker (ARB) which can be optionally derivatized to also fully or partially activate PPARγ are heterocyclic benzimidazoles (United States Pat. No. 6,100,252).

[0006] Compounds, such as those above, which are full agonists of PPARγ may be used to treat and/or prevent type 2 diabetes and a variety of other disorders. However, those compounds that fully activate PPARγ are associated with numerous adverse

effects (*e.g.*, weightgain, fluid retention, peripheral edema, pulmonary edema and congestive heart failure) which limits the clinical utility of these ligands.

[0007] In contrast to full PPARγ agonists, PPARγ partial agonists or synthetic PPARγ modulators (SPPARMs) may possess substantial efficacy with reduced side-effect profiles, including diminished potential for weight gain, fluid retention and edema.

[0008] Accordingly, what is needed are novel compounds which are PPARγ partial agonists. Ideally, these compounds may be used to treat and/or prevent type 2 diabetes and a variety of other disorders without significant side effects. The PPARγ partial agonists may also inhibit the angiotensin II type 1 receptor (AT1).

3. Summary

[0009] The present invention satisfies these and other needs by providing novel compounds which at least partially activate PPARγ and may further inhibit the activity of the AT1 receptor. The novel compounds include compounds of Formulae I and II, *infra*.

[0010] In a second aspect, the present invention provides pharmaceutical compositions of compounds of Formulae I and II, *infra*. The pharmaceutical compositions generally comprise one or more compounds of Formulae I and/or II and a pharmaceutically acceptable vehicle. In a preferred embodiment, the pharmaceutical compositions are for the treatment or prevention of a family of related metabolic disorders in a mammal, particularly a disorder selected from the group consisting of type 2 diabetes and the metabolic syndrome.

[0011] In a third aspect, the present invention provides methods for treating or prophylactically preventing an inflammatory or metabolic disorder in a mammal comprising administering to the mammal in need thereof, a therapeutically effective amount of a compound sufficient to at least partially activate a peroxisome proliferator-activated receptor (PPAR), in particular PPARγ. These methods can be used for treating or preventing a variety of inflammatory and proliferative diseases (see Tables I-X, *infra*), including but not limited to, type 2 diabetes and metabolic syndrome. The methods generally involve administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of Formulae I and/or II, *infra*.

[0012] In a fourth aspect, the current invention provides methods of screening a compound for capability to treat or prevent an inflammatory or metabolic disorder in a mammal, the method comprising: (a) identifying a compound as at least partially activating a peroxisome proliferator-activated receptor (PPAR), particularly PPARγ; (b) identifying the compound as at least partially inhibiting an activity of angiotensin II type 1 receptors; and (c) selecting the compound as capable of treating or preventing an inflammatory or metabolic disorder. These methods may further comprise selecting a compound that does not cause, promote, or aggravate at least one of fluid retention, peripheral edema; pulmonary edema, and congestive heart failure in the mammal.

4. Detailed Description

4.1 Definitions

[0013] "Compounds" refers to any compounds encompassed by generic formulae disclosed herein. Compounds may be identified either by their chemical structure and/or chemical name. When the chemical structure and chemical name conflict, the chemical structure is determinative of the identity of the compound. The compounds described herein may contain one or more chiral centers and/or double bonds and therefore, may exist as stereoisomers, such as double-bond isomers (*i.e.*, geometric isomers), enantiomers or diastereomers. Accordingly, the chemical structures depicted herein encompass all possible enantiomers and stereoisomers of the illustrated compounds including the stereoisomerically pure form (*e.g.*, geometrically pure, enantiomerically pure or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well known to the skilled artisan. The compounds may also exist in several tautomeric forms including the enol form, the keto form and mixtures thereof. Accordingly, the chemical structures depicted herein encompass all possible tautomeric forms of the illustrated compounds. The compounds described also include isotopically labeled compounds where one or more atoms have an atomic mass different from the atomic mass conventionally found in nature. Examples of isotopes that may be incorporated into the compounds of the invention include, but

are not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, *etc.* Compounds may exist in unsolvated forms as well as solvated forms, including hydrated forms and as N-oxides. In general, compounds may be hydrated, solvated or N-oxides. Certain compounds may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated herein and are intended to be within the scope of the present invention. Further, it should be understood, when partial structures of the compounds are illustrated, that brackets indicate the point of attachment of the partial structure to the rest of the molecule.

[0014] The term "alkyl" refers to a monovalent, saturated aliphatic hydrocarbon radical having the indicated number of carbon atoms and that is optionally substituted. For example, a "C 1-6 alkyl" or an "alkyl of 1-6 carbons" or "Alk 1-6 would refer to any alkyl group containing one to six carbons in the structure. "C 1-20 alkyl" refer to any alkyl group having one to twenty carbons. Alkyl may be a straight chain (i.e. linear) or a branched chain. Lower alkyl refers to an alkyl of 1-6 carbons. Representative examples lower alkyl radicals include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isopropyl, isobutyl, isopentyl, amyl, sec-butyl, tert-butyl, tert-pentyl and the like. Higher alkyl refers to alkyls of seven carbons and above. These include n-heptyl, n-octyl, n-nonyl, n-decyl, n-dodecyl, n-tetradecyl, n-hexadecyl, n-octadecyl, n-eicosyl, and the like, along with branched variations thereof. The radical may be optionally substituted with substituents at positions that do not significantly interfere with the preparation of compounds falling within the scope of this invention and that do not significantly reduce the efficacy of the compounds. The alkyl is optionally substituted with one to five substituents independently selected from the group consisting of halo, lower alkoxy, hydroxy, cyano, nitro, amino, halogenated lower alkyl, halogenated lower alkoxy, hydroxycarbonyl, lower alkoxycarbonyl, lower alkylcarbonyloxy, and lower alkylcarbonylamino.

[0015] "Alkenyl" by itself or as part of another substituent refers to an unsaturated branched, straight-chain, or cyclic aliphatic hydrocarbon radical having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene having the indicated number of carbon atoms, *e.g.* 1-20, preferably 1-6. The group may be in either the *cis* or *trans* conformation about the double bond(s). Typical alkenyl groups include, but are not limited to, ethenyl; propenyls such as prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), prop-2-en-2-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl; butenyls such as

but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, *etc.*; and the like. This radical is optionally substituted similarly to alkyl.

[0016] "Alkynyl" by itself or as part of another substituent refers to an unsaturated branched, straight-chain, or cyclic aliphatic hydrocarbon radical having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne having the indicated number of carbon atoms, *e.g.* 1-20, preferably 1-6. Typical alkynyl groups include, but are not limited to, ethynyl; propynyls such as prop-1-yn-1-yl, prop-2-yn-1-yl, *etc.*; butynyls such as but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, *etc.*; and the like. This radical is optionally substituted similarly to alkyl.

[0017] "Acyl" by itself or as part of another substituent refers to a radical $-C(O)R^{30}$, where R^{30} is hydrogen, alkyl, akenyl, alkynl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, or arylalkyl, as defined herein. Representative examples include, but are not limited to formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl, benzylcarbonyl and the like.

[0018] The term "alkoxy" refers to a monovalent radical of the formula RO-, where R is an alkyl as defined herein. Lower alkoxy refers to an alkoxy of 1-6 carbon atoms, with higher alkoxy is an alkoxy of seven or more carbon atoms. Representative lower alkoxy radicals include methoxy, ethoxy, n-propoxy, n-butoxy, n-pentyloxy, n-hexyloxy, isopropoxy, isobutoxy, isopentyloxy, amyloxy, sec-butoxy, tert-butoxy, tert-pentyloxy, and the like. Higher alkoxy radicals include those corresponding to the higher alkyl radicals set forth herein. The radical may be optionally substituted with substituents at positions that do not significantly interfere with the preparation of compounds falling within the scope of this invention and that do not significantly reduce the efficacy of the compounds. The alkyl is optionally substituted with one to five substituents independently selected from the group consisting of halo, lower alkyl, lower alkoxy, hydroxy, cyano, nitro, amino, halogenated lower alkyl, halogenated lower alkoxy, hydroxycarbonyl, lower alkoxycarbonyl, lower alkylcarbonyloxy, and lower alkylcarbonylamino.

[0019] "Alkoxycarbonyl" by itself or as part of another substituent refers to a radical $-C(O)OR^{32}$ where R^{32} represents an alkyl or cycloalkyl group as defined herein. Representative examples include, but are not limited to, methoxycarbonyl,

ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, cyclohexyloxycarbonyl and the like.

[0020] The term "alkylcarboxyloxy" is a monovalent radical having the formula -OC(O)Alk, where Alk is alkyl, preferably lower alkyl.

[0021] The term "alkylcarbonylamino" is a monovalent radical having the formula -NHC(O)Alk, where Alk is alkyl, preferably lower alkyl.

[0022] "Alkylsulfinyl" by itself or as part of another substituent refers to the radical $R^{33}SO$- where R^{33} is hydrogen, alkyl, cycloalkyl or aryl as defined herein.

[0023] "Alkylsulfonyl" by itself or as part of another substituent refers to the radical $R^{33}SO_2$- where R^{33} is hydrogen, alkyl, cycloalkyl or aryl as defined herein.

[0024] "Alkylsulfonylamino" by itself or as part of another substituent refers to the radical $-NR^{33}SO_2R^{34}$ where R^{33} and R^{34} independently are hydrogen, alkyl, cycloalkyl or aryl as defined herein.

[0025] "Alkylthio" by itself or as part of another substituent refers to the radical $-SR^{33}$ where R^{33} is hydrogen, alkyl, cycloalkyl or aryl as defined herein.

[0026] "Amido" by itself or as part of another substituent refers to the radical $-NR^{33}C(O)OH$ where R^{33} is hydrogen, alkyl, cycloalkyl or aryl as defined herein.

[0027] "Amino" by itself or as part of another substituent refers to the radical $-NR^{34}R^{35}$ where R^{34} and R^{35} independently are hydrogen, alkyl, cycloalkyl or aryl as defined herein.

[0028] "Angiogenesis" refers to a process by which normally quiescent endothelium responds to physiological or pathological stimuli (such as proliferating endometrium, injury, tumor growth, or diabetic retinopathy) resulting in pathological proliferation of blood vessels (neovascularization). Pathological angiogenesis (neovascularization) results in inappropriate vascular proliferation as in tumor neovascularization, lymphangiogenesis, tumor metastasis, *etc.*

[0029] "Angiotensin II-dependent disease" refers to a disease in which: 1) administration of a AT1 receptor antagonist slows, ameliorates, stops or reverses the pathological process, and/or 2) said disease is associated with impaired signal transduction within the rennin-angiotensin-aldosterone-system (RAAS) system, and/or 3) said disease is facilitated or exacerbated by activation of the AT1 receptor by angiotensin II, the initiating step being the by binding of angiotensin II the AT1 receptor.

[0030] "Aryl" by itself or as part of another substituent refers to a monovalent aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, phenyl, 1-naphthyl, 2-naphthyl, and the like. A "1-naphthyl" or "2-naphthyl" is a radical formed by removal of a hydrogen from the 1- or 2-position of a naphthalene structure, respectively. It is optionally substituted with from one to four substituents independently selected from the group consisting of halo, lower alkyl, lower alkoxy, hydroxy, cyano, nitro, amino, halogenated lower alkyl, formyl, halogenated lower alkoxy, hydroxycarbonyl, lower alkoxycarbonyl, lower alkylcarbonyloxy, and lower alkylcarbonylamino. A "phenyl" is a radical formed by removal of a hydrogen from a benzene ring. The phenyl is optionally substituted with from one to five substituents independently selected from the group consisting of halo, lower alkyl, lower alkoxy, hydroxy, cyano, nitro, amino, halogenated lower alkyl, halogenated lower alkoxy, carbonyl, hydroxycarbonyl, lower alkylcarbonyloxy, benzyloxy, optionally substituted piperidino, lower alkoxycarbonyl, and lower alkylcarbonylamino.

[0031] "Arylalkyl" by itself or as part of another substituent refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl group. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenyleth-1-yl, naphthylmethyl, 2-naphthyleth-1-yl, naphthobenzyl, 2-naphthophenyleth-1-yl and the like. Preferably, an arylalkyl group is (C_6-C_{30}) arylalkyl, *e.g.*, the alkyl moiety of the arylalkyl group is (C_1-C_{10}) and the aryl moiety is (C_6-C_{20}). More preferably, an arylkyl group is (C_6-C_{20}) arylalkyl, *e.g.*, the alkyl moiety of the arylalkyl group is (C_1-C_8) and the aryl moiety is (C_6-C_{12}).

[0032] "Body mass index" (BMI) refers to the weight in kilograms of a patient divided by the square of the height in meters, such that BMI has units of kg/m^2.

[0033] "Carbamoyl" by itself or as part of another substituent refers to the radical $-C(O)NR^{64}R^{65}$ where R^{64} and R^{65} are independently H-, alkyl, cycloalkyl, aryl, alkenyl, or alkynyl, or R^{64} and R^{65} together with the nitrogen atom form a cyclic amino.

[0034] "Carbamoyloxy" by itself or as part of another substituent refers to the radical $-OC(O)NR^{40}R^{41}$ where each of R^{40} and R^{41} is independently hydrogen, lower alkyl, hydroxy lower alkyl, alkoxy lower alkyl, amino lower alkyl, lower cycloalkyl, phenyl

(substituted or unsubstituted), or benzyl (substituted or unsubstituted), or where R^{40} and R^{41} together form a cyclic amino with the nitrogen atom. Examples include aminocarbonyloxy, methylaminocarbonyloxy, dimethyl aminocarbonyloxy, [4- (1-piperidino)- 1-piperidino] carbonyloxy, 1-morpholinocarbonyloxy, 1-pyrrolidinyl, 1-piperazinecarbonyloxy, and the like.

[0035] Congestive heart failure" (HF) refers to heart failure of any etiology, including but not limited to, heart failure with diastolic dysfunction, heart failure with systolic dysfunction, heart failure associated with cardiac hypertrophy, and heart failure that develops as a result of infectious myocarditis, inflammatory myocarditis, chemical myocarditis, cardiomyopathy of any etiology, hypertrophic cardiomyopathy, congenital cardiomyopathy, and cardiomyopathy associated with ischemic heart disease or myocardial infarction.

[0036] The term "cycloalkyl" refers to a monovalent, alicyclic, saturated hydrocarbon radical having three or more carbons forming the ring. While known cycloalkyl compounds may have up to 30 or more carbon atoms, generally there will be three to seven carbons in the ring. The latter include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. The radical may be optionally substituted with substituents at positions that do not significantly interfere with the preparation of compounds falling within the scope of this invention and that do not significantly reduce the efficacy of the compounds. The cycloalkyl is optionally substituted with one to five substituents independently selected from the group consisting of halo, lower alkyl, lower alkoxy, hydroxy, cyano, nitro, amino, halogenated lower alkyl, halogenated lower alkoxy, hydroxycarbonyl, lower alkoxycarbonyl, lower alkylcarbonyloxy, and lower alkylcarbonylamino.

[0037] A "cyclic amino" is a monovalent radical of saturated 5-, 6-, or 7-membered cyclic amine ring having no more than one additional hetero atom such as nitrogen, oxygen, or sulfur. Representative examples include, *e.g.*, 1-pyrrolidino, 1-piperidino, morpholino, piperazino, and the like. These may be substituted or unsubstituted. If substituted, generally they will have no more than 2 substituents chosen from lower alkyl, lower cycloalkyl, hydroxy lower alkyl, phenyl (substituted or unsubstituted), benyzl (substituted or unsubstituted), aminocarbonylmethyl, lower alkylaminocarbonylmethyl, amino, mono-or di-lower alkylamino, or cyclic amino.

[0038] "Degenerative disease" refers to a disease associated with deterioration or destruction normal tissue, resulting from immune dysregulation resulting in the

upregulation of one or more inflammatory nuclear transcription factors, inflammatory cytokines and other inflammatory molecules such as proteases (*e.g.*, MMP-9) and iNOS, leading to pathological degeneration of the respective cell or tissue or organ which is the therapeutic target.

[0039] "Euglycemia" refers to a condition in which a patient has a fasting blood glucose concentration within the normal range, greater than 70 mg/dl (3.89 mmol/L) and less than 110 mg/dl (6.11 mmol/L).

[0040] A "fused 2-, 3-, or 4-ring heterocyclic radical" is polynuclear in that the adjacent rings share a pair of atoms, generally carbon atoms. At least one of the rings will be heterocyclic in that it will have a noncarbon atom such as nitrogen, oxygen, or sulfur. The ring system may contain from 9 to 18 atoms. A 2-ring heterocyclic system will generally have 9 or 10 atoms included in the ring. Examples of such a 2-ring system include benzimidazole, quinoline, isoquinoline, purine, indolizine, 4H-quinolizine, 3H-pyrrolizine, coumaran, coumarin, isocoumarin, 4-methylcoumarin, 3-chloro-H-methylcoumarin, chromone, benzofuran, benzothiophene, benzothiazole, indole, and the like. A 3-ring system will generally have 12 to 14 atoms included in the ring. Examples of such a 3-ring system include carbazole, acridine, and the like. A 4-ring fused system will generally have 16 to 18 atoms included in the chain. Examples of such a 4-ring system include isothebaine and the like. The ring is bonded through a carbon in the ring system. The radical may be optionally substituted with substituents at positions that do not significantly interfere with the preparation of compounds falling within the scope of this invention and that do not significantly reduce the efficacy of the compounds. The radical is optionally substituted with one to five substituents independently selected from the group consisting of halo, lower alkyl, lower alkoxy, hydroxy, cyano, nitro, amino, halogenated lower alkyl, halogenated lower alkoxy, hydroxycarbonyl, lower alkoxycarbonyl, lower alkylcarbonyloxy, and lower alkylcarbonylamino.

[0041] A "halo" substitutent is a monovalent halogen radical chosen from chloro, bromo, iodo, and fluoro. A "halogenated" compound is one substituted with one or more halo substituent.

[0042] "Heart failure" includes congestive heart failure, heart failure with diastolic dysfunction, heart failure with systolic dysfunction, heart failure associated with cardiac hypertrophy, and heart failure that develops as a result of chemically induced

cardiomyopathy, congenital cardiomyopathy, and cardiomyopathy associated with ischemic heart disease or myocardial infarction.

[0043] A "5-membered heterocyclic ring" is a monovalent radical of a 5-member closed ring containing carbon and at least one other element, generally nitrogen, oxygen, or sulfur and may be fully saturated, partially saturated, or unsaturated (i.e. aromatic in nature). Generally the heterocycle will contain no more than two hetero atoms. Representative examples of unsaturated 5-membered heterocycles with only one hetero atom include 2- or 3-pyrrolyl, 2- or 3-furanyl, and 2- or 3-thiophenyl. Corresponding partially saturated or fully saturated radicals include 3-pyrrolin-2-yl, 2- or 3-pyrrolidinyl, 2- or 3-tetrahydrofuranyl, and 2- or 3-tetrahydrothiophenyl. Representative unsaturated 5-membered heterocyclic radicals having two hetero atoms include imidazolyl, oxazolyl, thiazolyl, pyrazolyl, tetrazolyl and the like. The corresponding fully saturated and partially saturated radicals are also included. The heterocyclic radical is bonded through an available carbon atom in the heteocyclic ring. The radical may be optionally substituted with substituents at positions that do not significantly interfere with the preparation of compounds falling within the scope of this invention and that do not significantly reduce the efficacy of the compounds. The ring is optionally substituted with one or two substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, hydroxy, cyano, nitro, amino, halogenated lower alkyl, halogenated lower alkoxy, hydroxycarbonyl, lower alkoxycarbonyl, lower alkylcarbonyloxy, and lower alkylcarbonylamino.

[0044] A "6-membered heterocyclic ring" is a monovalent radical of a 6-member closed ring containing carbon and at least one other element, generally nitrogen, oxygen, or sulfur and may be fully saturated, partially saturated, or unsaturated (i.e. aromatic in nature). Generally the heterocycle will contain no more than two hetero atoms. Representative examples of unsaturated 6-membered heterocycles with only one hetero atom include 2-, 3-, or 4-pyridinyl, 2H-pyranyl, and 4H-pryanyl. Corresponding partially saturated or fully saturated radicals include 2-, 3-, or 4-piperidinyl, 2-, 3-, or 4-tetrahydropyranyl and the like. Representative unsaturated 6-membered heterocyclic radicals having two hetero atoms include 3- or 4- pyridazinyl, 2-, 4-, or 5- pyrimidinyl, 2-pyrazinyl, and the like. The corresponding fully saturated and partially saturated radicals are also included, *e.g.* 2–piperazine. The heterocyclic radical is bonded through an available carbon atom in the heterocyclic ring. The

radical may be optionally substituted with substituents at positions that do not significantly interfere with the preparation of compounds falling within the scope of this invention and that do not significantly reduce the efficacy of the compounds. The ring is optionally substituted with one or two substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, hydroxy, cyano, nitro, amino, halogenated lower alkyl, halogenated lower alkoxy, hydroxycarbonyl, lower alkoxycarbonyl, lower alkylcarbonyloxy, and lower alkylcarbonylamino.

[0045] The term "hydroxycarbonyl" is a monovolent radical having the formula –C(O)OH.

[0046] "Inflammatory disease" refers to a disease associated dysfunction of the immune system, exemplified as, but not limited to: 1) increased production of inflammatory cytokines (interleukin (IL)-1beta, IL-2, IL-6, IL-8, IL-12, tumor necrosis factor-α, interferon-γ, monocyte chemoattractant protein-1), 2) increased conversion of Th2 lymphocytes to the Th1 phenotype or increased Th1/Th2 ratio, 3) inappropriate function of NK (killer) T lymphocytes resulting in auto-antibodies and lack of "self" recognition resulting in an autoimmune disease, 4) increased expression or activation of inflammatory nuclear transcription factors (NFAT, NF-κB, AP-1, JNK/STAT), 5) increased expression of iNOS.

[0047] "Insulin resistance" refers to a condition in which circulating insulin levels in excess of the normal response to a glucose load are required to maintain the euglycemic state (Ford *et al.*, *JAMA.* 2002, 287:356-9). Insulin resistance and the response of a patient with insulin resistance to therapy, may be quantified by assessing the homeostasis model assessment to insulin resistance (HOMA-IR) score, a reliable indicator of insulin resistance (Katsuki *et al.*, *Diabetes Care* **2001**, 24:362-5). An estimate of insulin resistance by the homeostasis assessment model (HOMA)-IR score may be calculated by a formula disclosed in Galvin *et al.*, *Diabet Med* **1992**, 9:921-8 where HOMA-IR = [fasting serum insulin (μU/mL)] x [fasting plasma glucose (mmol/L)/22.5].

[0048] "Hyperinsulinemia" is defined as the condition in which a subject with insulin resistance, with or without euglycemia, in which the fasting or postprandial serum or plasma insulin concentration is elevated above that of normal, lean individuals without insulin resistance, having a waist-to-hip ration < 1.0 (for men) or < 0.8 (for women).

[0049] "Impaired glucose tolerance" (IGT), refers to a condition in which a patient has a fasting blood glucose concentration or fasting serum glucose concentration greater than 110 mg/dl and less than 126 mg/dl (7.00 mmol/L), or a 2 hour postprandial blood glucose or serum glucose concentration greater than 140 mg/dl (7.78 mmol/L) and less than 200 mg/dl (11.11 mmol/L).

[0050] "Metabolic syndrome" is a syndrome complex consisting of multiple clinical conditions and risk factors that stratify together. The cardinal feature of the metabolic syndrome is insulin resistance (Laaksonen et al., Am J Epidemiol 2002, 156:1070-7). In one aspect, according to the ATP III/NCEP guidelines (Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) JAMA: Journal of the American Medical Association (2001) 285:2486-2497), diagnosis of the metabolic syndrome is made when three or more of the following risk factors are present:

1. Abdominal obesity, defined as waist circumference > 40 inches or 102 cm in men, and > 35 inches or 94 cm in women
2. Triglycerides: $\geq$ 150 mg/dL
3. HDL-cholesterol < 40 mg/dL in men
4. Blood pressure $\geq$ 130/85 mm Hg (SBP $\geq$ 130 or DBP $\geq$ 85)
5. Fasting blood glucose $\geq$ 110 mg/dL

[0051] In other aspects, the metabolic syndrome is described by accepted synonyms, which includes, but is not limited to, syndrome X, insulin resistance syndrome, insulin-resistant hypertension, the metabolic hypertensive syndrome, dysmetabolic syndrome. Components of the metabolic syndrome include, but is not limited to, glucose intolerance, impaired glucose tolerance, impaired fasting serum glucose, impaired fasting blood glucose, hyperinsulinemia, pre-diabetes, obesity, visceral obesity, hypertriglyceridemia, elevated serum concentrations of free fatty acids, elevated serum concentrations of C-reactive protein, elevated serum concentrations of lipoprotein(a), elevated serum concentrations of homocysteine, elevated serum concentrations of small, dense low-density lipoprotein (LDL)-cholesterol, elevated serum concentrations of lipoprotein-associated phospholipase (A2), reduced serum concentrations of high density lipoprotein (HDL)-cholesterol, reduced serum

concentrations of HDL(2b)-cholesterol, reduced serum concentrations of adiponectin, and albuminuria (*see:* Pershadsingh HA. Peroxisome proliferator-activated receptor-gamma: therapeutic target for diseases beyond diabetes: quo vadis? *Expert Opin Investig Drugs.* (2004) **13**:215-28, and references cited therein).

[0052] "Negatively charged group" refers to a moiety having a negative charge, either localized or delocalized. The term "negatively charged also encompasses thosemoieties that can be metabolized *in vivo* to a moiety having a negative charge. Exemplary negatively charged groups include 2-tetrazolyl, carboxyl, alkoxycarbonyl, carbamoyl, sulfonamido, or alkylsulfonamido. A lower alkoxycarbonyl, for example, can be metabolized *in vivo* to carboxyl, which is a negatively charged group.

[0053] "Parent Aromatic Ring System" refers to an unsaturated cyclic or polycyclic ring system having a conjugated π electron system. Specifically included within the definition of "parent aromatic ring system" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, fluorene, indane, indene, phenalene, *etc.* Typical parent aromatic ring systems include, but are not limited to, aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like.

[0054] "Parent Heteroaromatic Ring System" refers to a parent aromatic ring system in which one or more carbon atoms (and any associated hydrogen atoms) are independently replaced with the same or different heteroatom. Typical heteroatoms to replace the carbon atoms include, but are not limited to, N, P, O, S, Si, *etc.* Specifically included within the definition of "parent heteroaromatic ring systems" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, arsindole, benzodioxan, benzofuran, chromane, chromene, indole, indoline, xanthene, *etc.* Typical parent heteroaromatic ring systems include, but are not limited to, arsindole, carbazole, β-carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline,

isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like.

[0055] "Proliferative disease" refers to a disease associated with: 1) pathological proliferation of normally quiescent cells, 2) pathological migration of cells from their normal location (*e.g.* metastasis of neoplastic cells), 3) pathological expression of proteolytic enzymes such as the matrix metalloproteinases (collagenases, gelatinases, elastases), 4) pathological angiogenesis as in proliferative retinopathy and tumor metastasis.

[0056] "Obesity" refers to the condition where a patient has a BMI equal to or greater than 30 kg/m^2.

[0057] "Overweight" refers to a patient with a BMI greater than or 25 kg/m^2 and less than 30 kg/m^2.

[0058] "Patient" refers to a mammal, which is preferably human.

[0059] "Pharmaceutically acceptable salt" refers to a salt of a compound, which possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like.

[0060] "Pharmaceutically acceptable vehicle" refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered.

[0061] "PPAR" refers to one or any combination of PPARα, PPARγ and PPARδ.

[0062] "PPARγ" refers one or any combination of ΠΠΑγ1, PPARγ2, PPARγ3.

[0063] "PPAR activator" or "PPARγ activator (agonist)" means any compound that, by any mechanism increases, or causes an increase in the activity of PPARγ or the heterodimer of PPARγ with the retinoid X receptor (RXR), either by direct binding to either PPARγ or RXR or indirectly through any other mechanism that affects the ability of PPARγ or the PPARγ-RXR heterodimer to influence gene expression. Such PPARγ activators may affect PPAR activity either alone or in combination with activation of other PPARs including either PPARα, PPARδ, or both PPARα and PPARδ.

[0064] "PPAR-dependent disease" refers to a disease in which 1) administration of a PPAR ligand slows, ameliorates, stops or reverses the pathological process, and/or 2) said disease is associated with impaired signal transduction upstream from PPAR and its interaction with the gene transcription machinery, and/or 3) activation, partial activation or antagonism by a PPAR ligand (PPARα, PPARγ, PPARδ) leads to the prevention, amelioration, cure, or arrest of said disease or pathological process.

[0065] "Pre-diabetes" refers to a condition where a patient is pre-disposed to the development of type 2 diabetes. P re-diabetes extends the definition of impaired glucose tolerance to include individuals with a fasting blood glucose within the high normal range $\geq$ 100 mg/dL (Meigs *et al.*, *Diabetes* **2003** 52:1475-1484) and fasting hyperinsulinemia (elevated plasma insulin concentration).

[0066] "Preventing" or "prevention" refers to a reduction in risk of acquiring a disease or disorder (*i.e.*, causing at least one of the clinical symptoms of the disease not to develop in a patient that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease).

[0067] "Prodrug" refers to a molecule that requires a transformation within the body to release a drug having a specific activity or to be converted to the drug having a specific activity. Prodrugs are frequently, although not necessarily, pharmacologically inactive until converted to the active drug. In some cases a prodrug may have an activity that is different from the activity of the entity into which it is converted. A hydroxyl containing molecule may form, for example, a sulfonate,

ester or carbonate prodrug, which may be hydrolyzed *in vivo* to provide the hydroxyl compound. An amino containing molecule may form, for example, a carbamate, amide, enamine, imine, N-phosphonyl, N-phosphoryl or N-sulfenyl prodrug, which may be hydrolyzed *in vivo* to provide the amino compound. A carboxylic acid molecule may form an ester (including silyl esters and thioesters), amide or hydrazide prodrug, which may be hydrolyzed *in vivo* to provide the carboxylic acid compound. Prodrugs for drugs which have functional groups different than those listed above are well known to the skilled artisan.

[0068] "Promoiety" refers to a form of protecting group that when used to mask a functional group within a drug molecule converts the drug into a prodrug. Typically, the promoiety will be attached to the drug *via* bond(s) that are cleaved by enzymatic or non-enzymatic means *in vivo*.

[0069] "Protecting group" refers to a grouping of atoms that when attached to a reactive functional group in a molecule masks, reduces or prevents reactivity of the functional group. Examples of protecting groups can be found in Green *et al.*, "Protective Groups in Organic Chemistry", (Wiley, 2nd ed. 1991) and Harrison *et al.*, "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996). Representative amino protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), *tert*-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("SES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("FMOC"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxy protecting groups include, but are not limited to, those where the hydroxy group is either acylated or alkylated such as benzyl, and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers and allyl ethers.

[0070] "Substituted" refers to a group in which one or more hydrogen atoms are independently replaced with the same or different substituent(s). Typical substituents include, but are not limited to, those substituents previously defined herein and others. Those include -M, $-R^{60}$, $-O^-$, =O, $-OR^{60}$, $-SR^{60}$, $-S^-$, =S, $-NR^{60}R^{61}$, $=NR^{60}$, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)_2O^-$, $-S(O)_2OH$, $-S(O)_2R^{60}$, $-OS(O_2)O^-$, $-OS(O)_2R^{60}$, $-P(O)(O^-)_2$, $-P(O)(OR^{60})(O^-)$, $-OP(O)(OR^{60})(OR^{61})$, $-C(O)R^{60}$, $-C(S)R^{60}$, $-C(O)OR^{60}$, $-C(O)NR^{60}R^{61}$,$-C(O)O^-$, $-C(S)OR^{60}$, $-NR^{62}C(O)NR^{60}R^{61}$, $-NR^{62}C(S)NR^{60}R^{61}$, $-NR^{62}C(NR^{63})NR^{60}R^{61}$ and $-C(NR^{62})NR^{60}R^{61}$ where M is

independently a halogen; R^{60}, R^{61}, R^{62} and R^{63} are independently hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, cyclic amino, fused 2-, 3-, or 4- ring heterocycle, a 5- or 6-membered heterocyclic ring, or optionally R^{60} and R^{61} together with the nitrogen atom to which they are bonded form a cyclic amine ring; and R^{64} and R^{65} are independently hydrogen, alkyl, substituted alkyl, aryl, cycloalkyl, substituted cycloalkyl, substituted aryl, and the like, or optionally R^{64} and R^{65} together with the nitrogen atom to which they are bonded form a cyclic amine ring. Preferably, substituents include -M, $-R^{60}$, =O, $-OR^{60}$, $-SR^{60}$, $-S^-$, =S, $-NR^{60}R^{61}$, $=NR^{60}$, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)_2R^{60}$, $-OS(O_2)O^-$, $-OS(O)_2R^{60}$, $-P(O)(O^-)_2$, $-P(O)(OR^{60})(O^-)$, $-OP(O)(OR^{60})(OR^{61})$, $-C(O)R^{60}$, $-C(S)R^{60}$, $-C(O)OR^{60}$, $-C(O)NR^{60}R^{61}$,$-C(O)O^-$, $-NR^{62}C(O)NR^{60}R^{61}$, more preferably, -M, $-R^{60}$, =O, $-OR^{60}$, $-SR^{60}$, $-NR^{60}R^{61}$, $-CF_3$, -CN, $-NO_2$, $-S(O)_2R^{60}$, $-P(O)(OR^{60})(O^-)$, $-OP(O)(OR^{60})(OR^{61})$, $-C(O)R^{60}$, $-C(O)OR^{60}$, $-C(O)NR^{60}R^{61}$,$-C(O)O^-$, most preferably, -M, $-R^{60}$, =O, $-OR^{60}$, $-SR^{60}$, $-NR^{60}R^{61}$, $-CF_3$, -CN, $-NO_2$, $-S(O)_2R^{60}$, $-OP(O)(OR^{60})(OR^{61})$, $-C(O)R^{60}$, $-C(O)OR^{60}$,$-C(O)O^-$, where R^{60}, R^{61} and R^{62} are as defined above.

[0071] "Treating" or "treatment" of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (*i.e.*, arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treating" or "treatment" refers to ameliorating at least one physical parameter, which may not be discernible by the patient. In yet another embodiment, "treating" or "treatment" refers to inhibiting the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter) or both. In yet another embodiment, "treating" or "treatment" refers to delaying the onset of the disease or disorder.

[0072] "Therapeutically effective amount" means the amount of a compound that, when administered to a patient for treating a disease, is sufficient to effect such treatment for the disease. When administered for preventing a disease, the amount is sufficient to avoid or delay onset of the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, *etc.*, of the patient to be treated.

[0073] "Thiocarboxy" by itself or as part of another substituent refers to the radical $-C(O)SR^{33}$ where R^{33} is hydrogen, alkyl, cycloalkyl or aryl as defined herein.

[0074] "Type 2 diabetes" refers to the condition in which a patient has a fasting blood glucose or serum glucose concentration greater than 125 mg/dl (6.94 mmol/L).

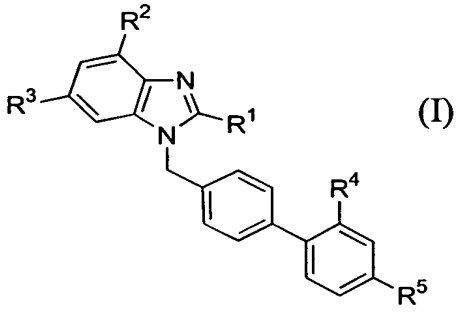
[0075] "Visceral obesity" refers to a waist to hip ration of 1.0 in male patients and 0.8 in female patients. In another aspect, visceral obesity defines the risk for insulin resistance and the development of pre-diabetes.

[0076] "Weight gain" refers to the increase in body weight in relationship to behavioral habits or addictions, *e.g.*, overeating or gluttony, smoking cessation, or in relationship to biological (life) changes, *e.g.*, weight gain associated with aging in men and menopause in women or weight gain after pregnancy.

[0077] Reference will now be made in detail to preferred embodiments of the invention. While the invention will be described in conjunction with the preferred embodiments, it will be understood that it is not intended to limit the invention to those preferred embodiments. To the contrary, it is intended to cover alternatives, modifications, and equivalents as may be included within the spirit and scope of the invention as defined by the appended claims.

4.2 Compounds

[0078] One aspect of the invention provides compounds of Formula I, which have the following structure:



(I)

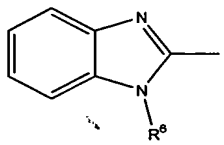
wherein R^1, R^2, and R^3 independently are hydrogen, hydroxy, halo, amino alkylamino, dialkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, acyl, alkoxycarbonyl, amido, alkoxy, thiocarboxy, carbamoyl, cyano, hydroxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, alkyl, alkenyl, alkynyl, aryl, 5- or 6- membered heterocyclic ring, or a fused 2-, 3-, or 4-membered heterocyclic

radical, and R^4 and R^5 independently are hydrogen, cyanate, or a negatively charged group.

In preferred aspects of the invention, the compound at least partially activates a PPAR, especially PPARγ. The compound may also inhibit the activity of angiotensin II type I receptor (AT1).

[0079] In a preferred embodiment of Formula I, R^1 is hydrogen, halogen, methoxy, hydroxyl, methyl, ethyl, or NH_2, R^2 is lower alkyl, R^3 is phenyl, a fused 2-membered heterocyclic radical or 5- or 6- membered heterocyclic ring, R^4 is a neutral group, and R^5 is a negatively charged group. More preferably, R^1 is hydrogen or methyl, R^2 is lower alkyl, R^3 is benzimidazole, R^4 is a hydrogen, and R^5 is alkoxycarbonyl or carboxyl.

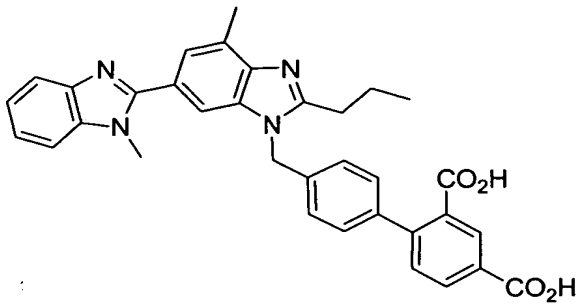
[0080] In yet another preferred embodiment of Formula I, R^3 is:



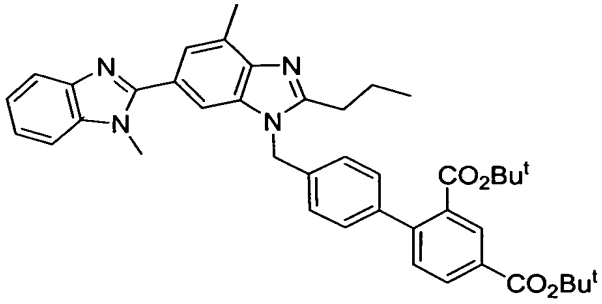
wherein R^6 is hydrogen, optionally substituted alkyl, halogen, amino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, acyl, alkoxycarbonyl, amido, alkoxy, thiocarboxy, or carbamoyl. Preferably, R^6 is hydrogen or lower alkyl.

[0081] In yet another preferred embodiment, R^1 is alkyl of 3 or more carbons, R^2 is hydrogen, hydroxy, halo, amino alkylamino, dialkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, acyl, alkoxycarbonyl, amido, alkoxy, thiocarboxy, carbamoyl, cyano, hydroxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, alkyl, alkenyl, alkynyl, aryl, 5- or 6- membered heterocyclic ring, or a fused 2-, 3-, or 4-membered heterocyclic radical, R^3 is aryl, 5- or 6- membered heterocyclic ring, or a fused 2-, 3-, or 4-membered heterocyclic radical, R^4 is a negatively charged group and R^5 is negatively charged. More preferably, R^1 is propyl or butyl, R^2 is lower alkyl, R^3 is phenyl, a fused 2-membered heterocyclic radical or 5- or 6- membered heterocyclic ring, R^4 is cyanate, 2-tetrazolyl, carboxyl, alkoxycarbonyl, carbamoyl, sulfonamido, or alkylsulfonamido, and R^5 is cyanate, 2-tetrazolyl, carboxyl, alkoxycarbonyl, carbamoyl, sulfonamido, or alkylsulfonamido. Even more preferably R^1 is propyl or butyl, R^2 is lower alkyl, R^3 is benzimidazole, R^4 is lower alkoxycarbonyl or carboxyl, and R^5 is lower alkoxycarbonyl or carboxyl.

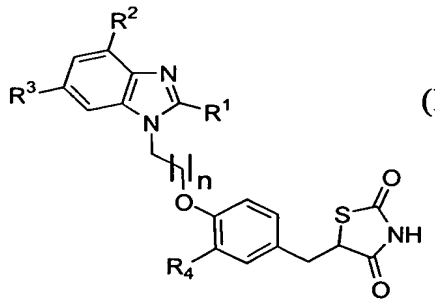
[0082] In a preferred embodiment, R^1 is n-propyl, R^2 is methyl, R^3 is 2-(N-Methylbenzimidazolyl), R^4 and R^5 are carboxyl, where the compound is:



[0083] In another preferred embodiment of Formula 1 R^1 is n-propyl, R^2 is methyl, R^3 is 2-(N-Methylbenzoimidazolyl), R^4 and R^5 are CO_2Bu^t, where the compound is:



[0084] Another aspect of the invention provides compounds of Formula II, which have the following structure:



(II)

wherein R^1, R^2, and R^3 independently are hydrogen, hydroxy, halo, amino alkylamino, dialkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, acyl, alkoxycarbonyl, amido, alkoxy, thiocarboxy, carbamoyl, cyano, hydroxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, alkyl, alkenyl, alkynyl, aryl,

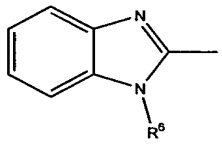
5- or 6- membered heterocyclic ring, or a fused 2-, 3-, or 4-membered heterocyclic radical;

n is 0 to 2; and

R^4 is hydrogen, cyanate, 2-tetrazolyl, carboxyl, alkoxycarbonyl, amido, or sulfonamido.

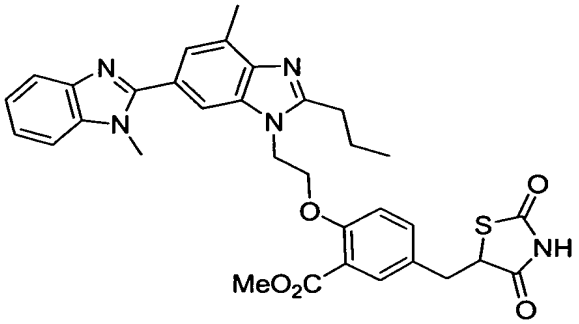
[0085] In a preferred embodiment of Formula II, R^1 is hydrogen, lower alkyl or cyclolower alkylalkyl, R^2 is hydrogen, lower alkyl, halogen, hydroxyl or NH_2, R^3 is phenyl, halogen, hydrogen, amino, alkoxy, hydroxyl, 5- or 6- membered heterocyclic ring, or a fused 2-4-membered heterocyclic radical, and R^4 is hydrogen, cyantate or a negatively charged group. More preferably, n is 1, R^1 is hydrogen, methyl, ethyl or 4-cyclohexylbutyl, R^2 is hydrogen, or methyl, R^3 is phenyl, halogen, or benzimidazole, and R^4 is loweralkoxycarbonyl or carboxyl.

[0086] In another preferred embodiment of Formula II, R^3 is

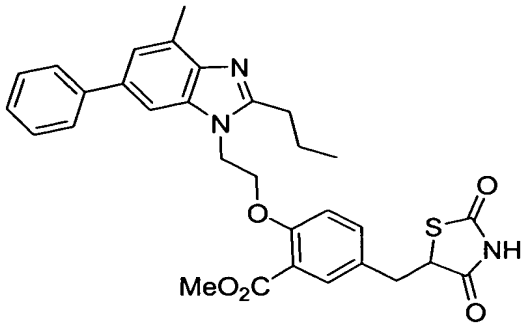


wherein R^6 is hydrogen, optionally substituted alkyl, halogen, amino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, acyl, alkoxycarbonyl, amido, alkoxy, thiocarboxy, or carbamoyl. More preferably, R^6 is hydrogen or lower alkyl.

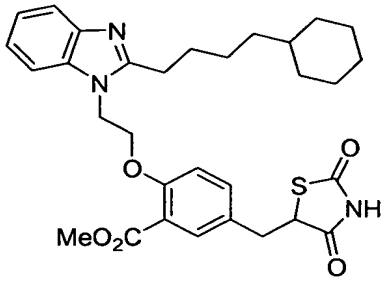
[0087] In a more particular embodiment of Formula II, R^1 is n-propyl, R^2 is methyl, R^3 is 2-(N-methylbenzoimidazolyl), n is one, and R^4 is methoxycarbonyl, where the compound is:



[0088] In another embodiment of Formula II, R^1 is n-propyl, R^2 is methyl, R^3 is phenyl, n is one, and R^4 is methoxycarbonyl, where the compound is:



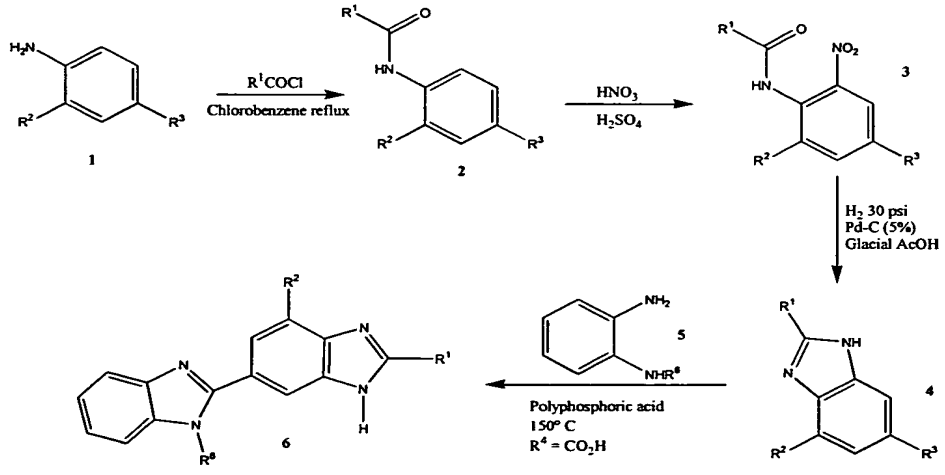
[0089] In yet another embodiment of Formula II, R^1 is 4-cyclohexybutyl, R^2 is hydrogen, R^3 is hydrogen, n is one, and R^4 is methoxycarbonyl, where the compound is:



4.3 Methods of Synthesis of Compounds of Formulae I and II

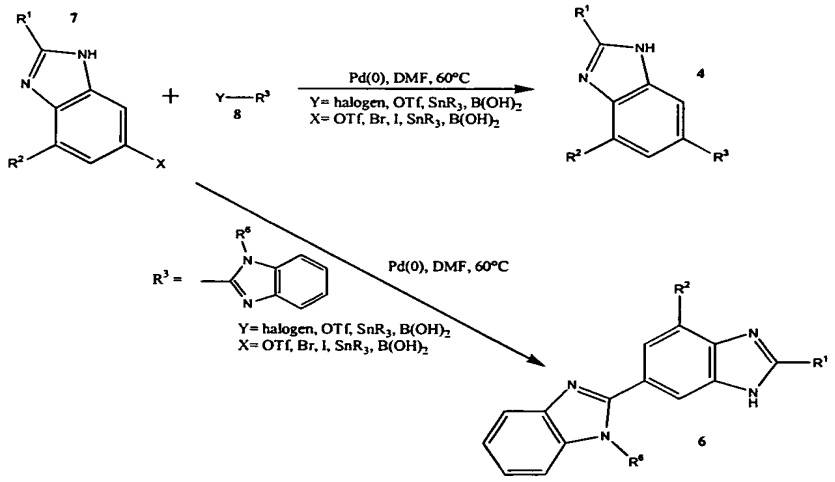
[0090] The compounds may be obtained *via* conventional synthetic methods illustrated in Schemes 1-7. Starting materials useful for preparing compounds of the invention and/or intermediates thereof are commercially available or can be prepared by well-known synthetic methods.

4.3.1 Scheme 1



[0091] Amino alkylcarboxylates such as **1**, wherein R^3 can correspond to a great variety of functionality, can be readily N-acylated to furnish anilides **2**. Nitration is conveniently ortho-directed by the amide N, while ortho nitration next to the carboxylate group is highly disfavored. The nitro species **3** is then reduced, conveniently by hydrogenation, or also by metal reduction (*e.g.*, Zn, HOAc; Sn, HCl) to afford the amine. Cyclization may occur under the conditions of the reaction, or if necessary, acetic acid can catalyze the cyclization to furnish the benzimidazole **4**. De-esterification can be accomplished by saponification with aqueous hydroxide, and the condensation with polyphosphoric acid (PPA) at higher temperatures in the presence of a orthophenylene diamine such as **5**, affords the desired biaryl compounds **6** (Zubarovskii, V. M.; Makovetskii, Yu. P. **Derivatives of benzimidazolylbenzimidazole.** *Ukrainskii Khimicheskii Zhurnal* (Russian Edition) **1968**, *34*(11), 1151-1155. Chem. Abstracts: ***70***: 68251; 2-Aralkyl-5-Arylbenzimidazoles. Chimetron S.a r.l. **1966**, 6 pp. FR 1450560 (Patent written in French). Chem. Abstracts: ***66***: 76010; Schneider, H.; **Regioselective nitration of aniline derivatives and benzimidazoles therefrom. 2000**, DE 19917524, 6 pp. Chem. Abstracts: ***133***:298017).

4.3.2 Scheme 2



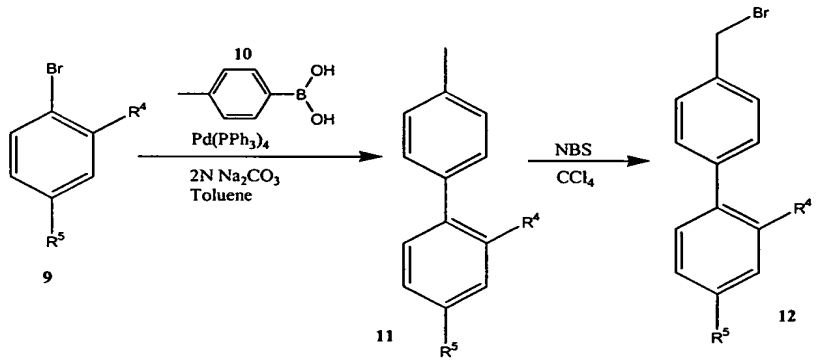
[0092] Another approach to the construction of the biaryl systems **6** could involve biaryl coupling chemistry *via* a 2-halobenzimidazole with a 6-activated benzimidazole

as shown in Scheme 2. The benzo-ring activated component, compound **7**, can have X = halogen (preferably), OTf, alkyltin, or boronic acid.

[0093] Alternatively, the Sn or B derivatives may need to be synthesized from either the OTf or Halogen derivatives if the appropriate starting materials are not practical or readily available. Assuming X is bromo, and then its synthesis should follow the outline in Scheme 2. Another benzimidazole, unsubstituted at C-2, can then be halogenated directly, or lithiated and captured with halogen, Sn or B derivatives. With the two benzimidazoles suitably activated (**7** and **8**), a Pd(0) catalyzed coupling should afford the same desired compounds outlined in Scheme 1.

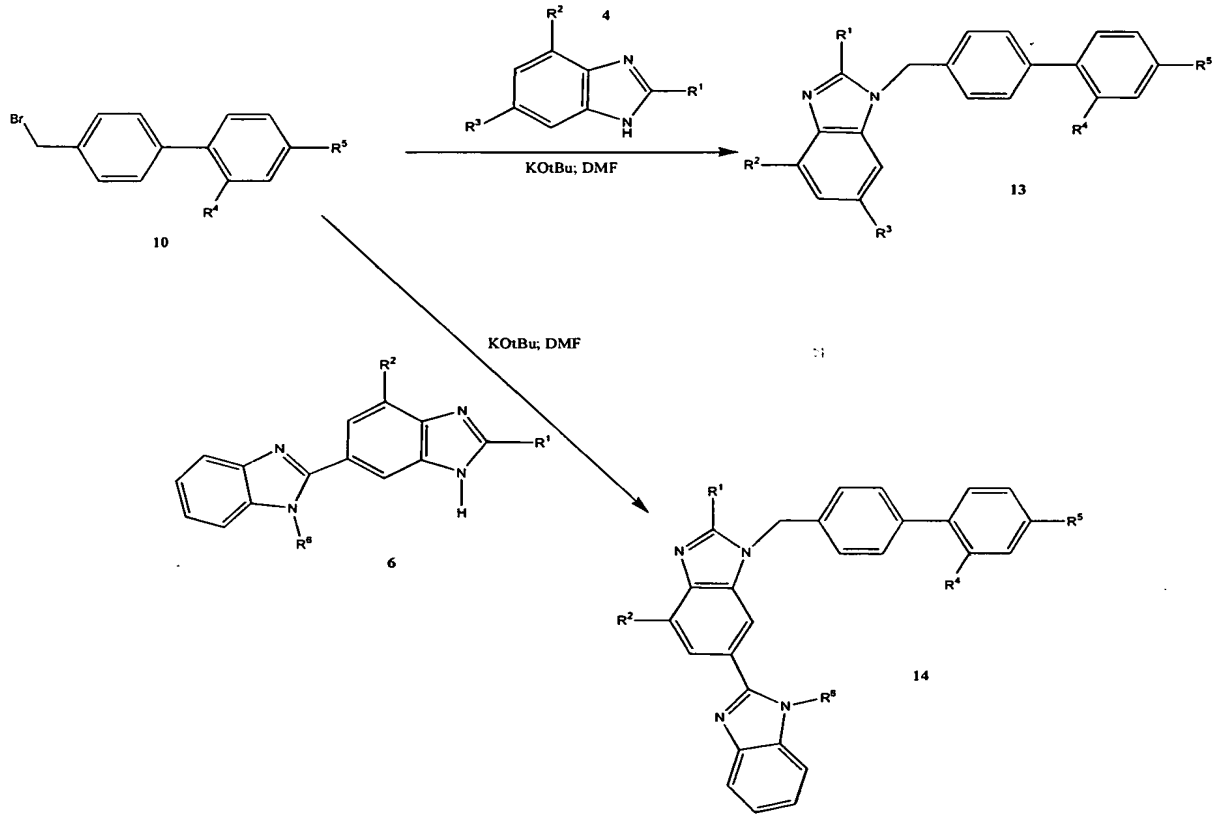
[0094] In certain cases, **7** may be coupled to provide examples wherein the second ring is not another benzimidazole, but any other substituted heterocycle, alkyl or aryl moiety, or other functionality [Ries, U.; Binder, K.; Zimmermann, R., **"Preparation of disubstituted bicyclic heterocyclic antithrombotics and anticoagulants"** Ger. Offen. (1998), 44 pp DE 19718181]. Hence, if **7** were coupled with phenylboronic acid, then **4**, a simplified version of **6** would be produced as shown in Scheme 2.

4.3.3 Scheme 3



[0095] For the construction of the biaryl systems **11** could involve biaryl coupling chemistry *via* a paratolulyl boronic acid with a halo 2,4-disubstituted benzenes as shown in Scheme 3. The benzo-ring activated component, compound **9**, can have X = halogen (preferably), OTf or alkyltin. Benzylic halogenation with N-halo succinamide in the presence of radical initiator such as azobisisobutyronitrile (AIBN) or benzoylperoxide could provide compound **12**.

4.3.4 Scheme 4



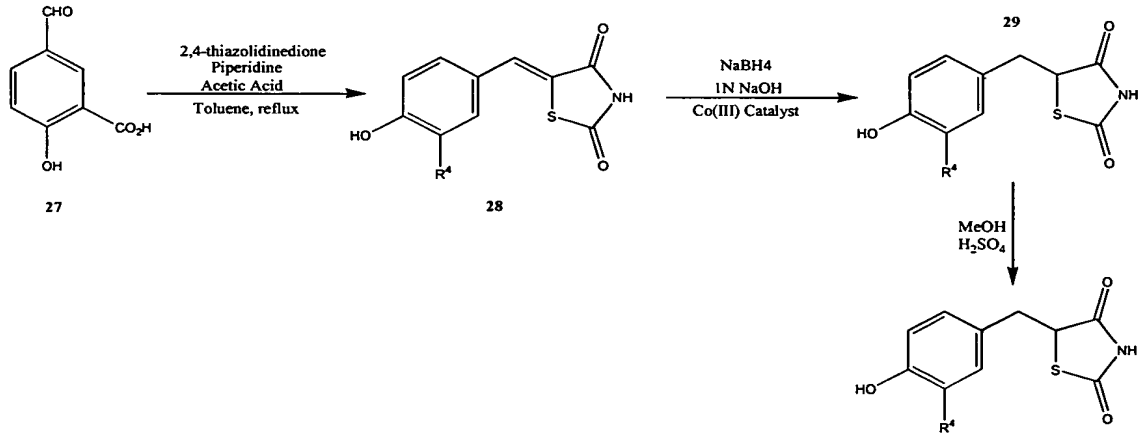
[0096] The synthesis of target compounds of Formula I is a variation of the approach used to prepare telmisartan **16**, also shown in Scheme 1 (Ries *et al.*, *Journal of Medicinal Chemistry* **1993**, *36*, 4040-4051; Hauel, *Eur. Pat. Appl.*; (Thomae, Dr. Karl, G.m.b.H., Germany). Ep, 1993; pp 25 pp; Hauel, *Ger. Offen.*; (Thomae, Dr. Karl, G.m.b.H., Germany). De, 1994; pp 23 pp.). Beginning with the reported 2-propyl-4,2'-dimethylbenzimidazolylbenzimidazole **6**, N-alkylation of the available benzimidazole ring nitrogen with the bromo-benzylbiaryl derivative **10** proceeds *via* the predominant/more reactive N-K tautomer (N-1 vs N-3) to afford **14**. Beginning with the more general benzimidazole derivative **4**, N-alkylation of the available benzimidazole ring nitrogen with the bromo-benzylbiaryl derivative **10** proceed via the predominant/more reactive N-K tautomer to afford **13**.

[0097] Now, carboxylic acid groups at R^4 and R^5 can be exposed by hydrolysis of the ester group under aqueous basic conditions. As stated above, the 2-propyl-4,2'-

dimethylbenzimidazolyl benzimidazole **6** can be synthesized, as shown in Schemes 1 or 2, in a manner analogous to that shown to afford general structures **14**. Furthermore, throughout these syntheses, cyano groups can often substitute for ester moieties at R^4 and R^5 on the bromo benzylbiaryl unit.

Exemplary derivatives of compound **14**					
R^1	R^2	R^4	R^5	R^6	**Compound**
n-propyl	methyl	CO_2Me	hydrogen	methyl	**15**
n-propyl	methyl	CO_2H	hydrogen	methyl	**16 (telmisartan)**
methyl	methyl	CO_2Me	hydrogen	methyl	**17**
methyl	methyl	CO_2H	hydrogen	methyl	**18**
n-propyl	methyl	CO_2Me	CO_2Me	methyl	**19**
n-propyl	methyl	CO_2H	CO_2H	methyl	**20**
methyl	methyl	CO_2Me	CO_2Me	methyl	**21**
methyl	methyl	CO_2H	CO_2H	methyl	**22 (averysartan)**
hydrogen	hydrogen	CO_2Me	hydrogen	hydrogen	**23**
hydrogen	hydrogen	CO_2H	hydrogen	hydrogen	**24**
hydrogen	methyl	CO_2Me	hydrogen	methyl	**25**
hydrogen	methyl	CO_2H	hydrogen	methyl	**26**

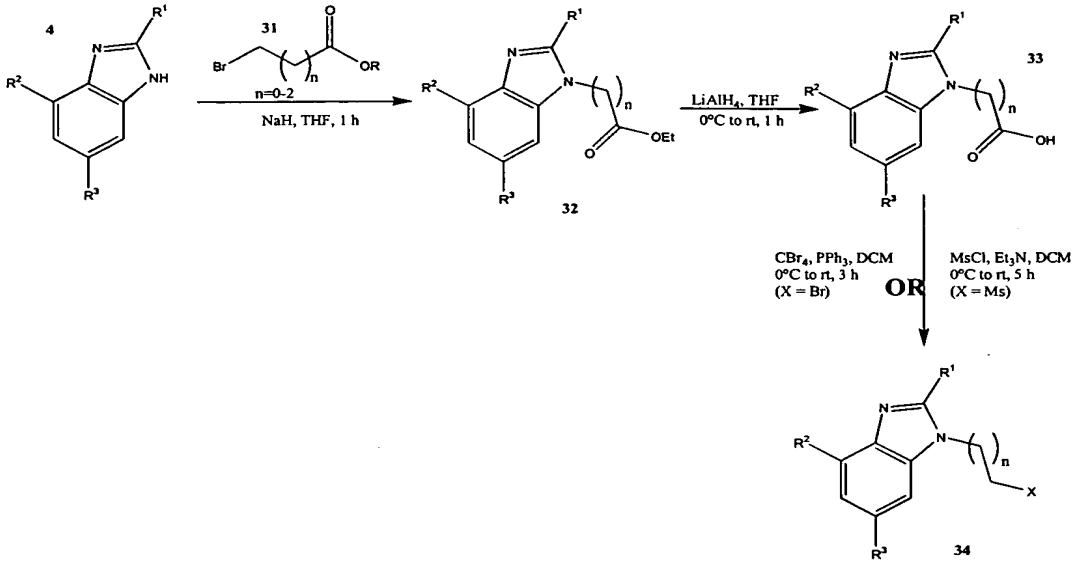
4.3.5 Scheme 5



[0098] For the preparation of compound **26** could involve Knoveneagel condensation of 2,4-thiazolidinedione with 5-formyl salicylic acid **27** in the presence of catalytic amount of piperidinylacetate. Cobalt (III) chloride catalyzed regiospecific reduction of the 5-benzylidene-2,4-thiazolidinediones using sodium borohydride (Ohnota, M.; Orita, K.; Aizawa, Y.; Yoshida, N.; Sakamaki, T., "Process for the preparation of

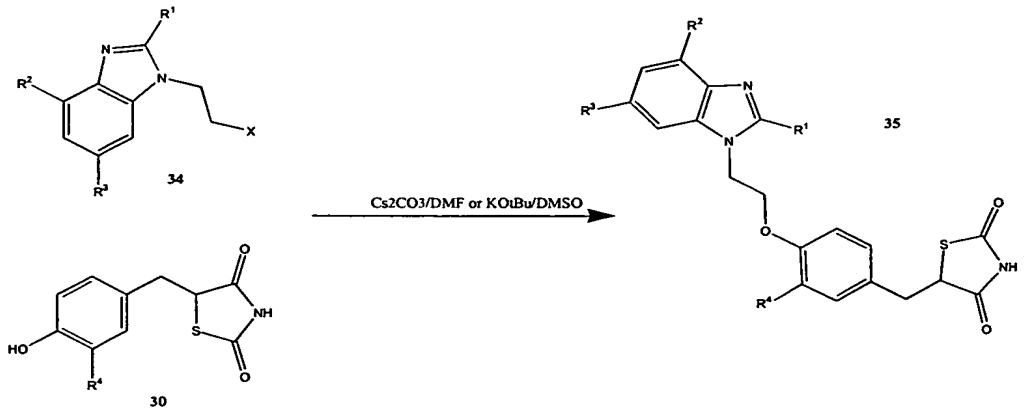
thiazolidinedione derivatives" PCT Int. Appl. **2001**, 17 pp. WO 2001096321) and esterification of the corresponding benzoic acid could provide compound **30**.

4.3.6 Scheme 6



[0099] Benzimidazoles such as **4**, wherein R_1, R_2, R_3 can correspond to a great variety of functionality, can be readily N-alkylated with bromo esters to furnish **32** [Shen, T-Y.; Dorn, C.P., Jr.; Grenda, V.J., "Antiviral 1,2-di-2-benzimidazolyl-1,2-ethanediols" Ger. Offen. (**1971**), DE 2038952]. The ester species is then reduced conveniently by metal hydride to afford alcohol **33**. The hydroxy group could be converted to a better leaving group such as bromide or mesylate **34**.

4.3.7 Scheme 7



[00100] Heterocyclic derivatives of Formula II could arise from simply coupling **34** with the appropriate heterocyclic phenol derivatives **30**. Attachment of

these side-chains via the appropriate heterocyclic phenol using Cs_2CO_3/DMF or KOtBu/DMSO provides the protected version of the target drugs **35**. Either conversion to pro-drug then ensues, or cleavage of the ester.

R^1	R^2	R^3	R^4	**Cmpd**
n-propyl	methyl	N-methylbenzoimidazolyl	CO_2Me	**36**
n-propyl	methyl	phenyl	CO_2Me	**37**
n-propyl	methyl	bromo	CO_2Me	**38**
n-propyl	methyl	bromo	CO_2Me	**39**
4-cyclohexylbutyl	hydrogen	hydrogen	CO_2Me	**40**

4.4 Therapeutic Methods of Use

[00101] One aspect of the invention provides methods for treating or preventing an inflammatory or metabolic disorder in a mammal comprising administering to the mammal in need thereof, a therapeutically effective amount of a compound sufficient to at least partially activate a peroxisome proliferator-activated receptor (PPAR).

[00102] In one embodiment, a compound of Formulae I or II and/or a pharmaceutical composition thereof is administered to a patient, preferably, a human, suffering from a disease listed in Tables I-X, *infra*. In another embodiment, a compound of Formulae I or II and/or pharmaceutical composition thereof is administered to a patient, preferably, a human, as a preventative measure against a disease listed in Tables I-X, *infra*.

TABLE I: Examples of dermatological disorders and inflammatory skin disorders treatable using compounds of this invention
Kertinizing skin diseases, keratitis, hidradenitis, ichthyosis, melasma
Psoriasis (including p. vulgaris, p. guttata, p. discoidea, p. anthropica, p. universalis)
Acne (including a. vulgaris, a. rosacea, a. inversa, cystic acne)
Warts, verrucae (common warts, anogenital (venereal) warts, viral warts including human papilloma virus (HPV) infections, conjunctival warts, oral/buccal warts)

Acute and chronic dermatitides (inflammation of the skin), atopic dermatitis, allergic dermatitis, contact dermatitis, cosmetic dermatitis, chemical dermatitis, seborrheic dermatitis, solar dermatitis, acute and chronic eczema, diaper rash, sunburn
Lupus associated skin lesions
Keratoses such as seborrheic keratosis, senile keratosis, actinic keratosis, photo-induced keratosis, skin aging, thinning skin, dry skin, wrinkle formation, photo-induced skin aging, keratosis follicularis
Keloids and prophylaxis against keloid formation
Leukoplakia, lichen planus
Urticaria, pruritus
Androgenic alopecia in men and women, hirsutism in women

TABLE II: Examples of psychiatric disorders treatable using compounds described in this invention
Depression, primary depression, depression secondary to chronic diseases, medications
Dysphoric mood disorders
Obsessive compulsive disorder
Dysthymic disorders
Manic depressive (unipolar or bipolar) disorder
Anxiety, panic disorder, agoraphobia
Post menstrual syndrome
Schizophrenia
Chronic fatigue syndrome
Substance abuse, drug addiction
Anorexia nervosa, anorexia bullemia

TABLE III: Examples of neurological/neurodegenerative disorders and CNS inflammatory disorders treatable using compounds described in this invention
Migraine headaches (*e.g.*, vascular headaches, common migraine)
Primary (*e.g.*, Alzheimer's disease) and secondary (*e.g.*, HIV-related) dementias
Degenerative CNS diseases (*e.g.*, Parkinson's disease, amyotropic lateral sclerosis)
Demyelinating diseases (*e.g.*, multiple sclerosis, Guillain-Barre syndrome)
Pain disorders including algesia, hyperalgesia, acute and chronic pain, allodynia
Primary and secondary encephalitis and encephalomyelitis (*e.g.*, autoimmune encephalomyelitis, allergic encephalomyelitis)
Primary and secondary neuritis, autoimmune neuritis
Other autoimmune diseases (*e.g.*, myesthenia gravis, Eaton-Lambert syndrome)
Congenital and secondary ataxias

TABLE IV: Examples of inflammatory and metabolic disorders associated with allograft transplantation treatable using compounds described in this invention
The compounds described herein are useful as monotherapy or adjunctive therapy with existing immunosuppressive agents for the promotion and maintenance of allograft survival, post-transplantation.
Examples of inflammatory and proliferative conditions or diseases associated with allograft transplantation and immune suppression include:
1. Acute allograft rejection
2. Chronic allograft rejection
3. Graft versus host disease
4. Post-transplantation de novo malignancy (*e.g.* lymphoma and epidermal cancers)
5. Osteoporosis and osteopenia
6. Hyperlipidemia
7. Insulin resistance and diabetes mellitus

8.	Hypertension
9.	Atherosclerosis
10.	Endarteritis associated with heart allograft transplantation
11.	Glomerulonephritis associated with renal allograft transplantation
12.	Cardiomyopathy and congestive heart failure associated with allograft transplantation, in particular heart transplantation

TABLE V: Examples of diseases of various organ systems treatable using compounds described in this invention

Organ System	*Disease/Pathology*
Cardiovascular	Metabolic disorders including hypertension, vasculo-occlusive diseases including atherosclerosis, arteritis, endarteritis, endocarditis, myocarditis, arterial plaque (fibrous cap) rupture, thrombosis, restenosis after any invasive vascular procedures; acute coronary syndromes such as unstable angina, myocardial infarction, myocardial ischemia and other ischemic cardiomyopathies, non-ischemic cardiomyopathies, post-myocardial infarction cardiomyopathy and myocardial fibrosis, drug-induced cardiomyopathy.
Endocrine	Metabolic disorders including obesity, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, impaired glucose tolerance, Cushing's syndrome (*e.g.* secondary to chronic glucocorticoid therapy), polycystic ovarian syndrome, osteoporosis, osteopenia, accelerated aging of tissues and organs, *e.g.*, Werner's syndrome.
Urogenital	Prostatitis, endometritis, endometriosis, benign prostatic hypertrophy, leiomyoma, polycystic kidney disease (*e.g.*, autosomal dominant PKD), acute tubular necrosis, nephrotic syndrome, diabetic nephropathy, glomerulonephritis, erectile dysfunction in men and women

Pulmonary	Asthma, chronic obstructive pulmonary disease (COPD), reactive airway disease, pulmonary fibrosis, pulmonary hypertension.
Connective tissue Joint	Rheumatoid arthritis, Raynaud's phenomenon/disease, Sjogren's syndrome, systemic sclerosis, systemic lupus erythematosus, inflammatory bowel disease (ulcerative colitis, Crohn's disease) vasculitides, ankylosing spondylitis, osteoarthritis, reactive arthritis, psoriatic arthritis, fibromyalgia, osteoarthritis, sarcoidosis.
Liver/Other	Hepatic fibrosis, hepatic cirrhosis, hepatic steatosis, all etiologies, *e.g.*, alcohol-induced (*e.g.*, ethanol), drug-induced (*e.g.*, tylenol), and toxin-induced (*e.g.*, mushroom poisoning) Fibrocystic breast disease, fibroadenoma, endometriosis

TABLE VIa: Examples of neoplastic diseases treatable using compounds described in this invention

Organ System	*Malignancy/Cancer type*
Skin	Basal cell carcinoma, melanoma, squamous cell carcinoma; cutaneous T cell lymphoma; Kaposi's sarcoma.
Hematological	Acute leukemia, chronic leukemia and myelodysplastic syndromes.
Urogenital	Prostatic, renal and bladder carcinomas, anogenital carcinomas including cervical, ovarian, uterine, vulvar, vaginal, and those associated with human papilloma virus infection.
Neurological	Gliomas including glioblastomas, astrocytoma, ependymoma, medulloblastoma, oligodendroma; meningioma, pituitary adenoma, neuroblastoma, craniopharyngioma.
Gastrointestinal	Colon, colorectal, gastric, esophageal, mucocutaneous carcinomas.
Breast	Breast cancer including estrogen receptor and progesterone receptor positive or negative subtypes, soft tissue tumors.

Metastasis	Metastases resulting from all neoplasms.
Other	Angiomata, angiogenesis associated with the neoplasms.

TABLE VIb: Examples of neoplastic diseases treatable using compounds described in this invention (cont'd)	
Location	*Malignancy/Cancer type*
Various	fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, enthotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelimoa, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma.

TABLE VII: Examples of viral infections and related pathologies treatable according to the methods of this invention	
Virus	*Viral infection/cancer or other virus-associated pathology*
HTLV	T-cell leukemia/lymphoma, HTLV-associated arthritides/myelopathies.
HPV	Cervical and anogenital cancers; common and anogenital (venereal) warts, including verrucae, condyloma or condyloma acuminata,

	related non-neoplastic (*e.g.*, keratitis, conjunctivitis) pre-neoplastic and neoplastic (*e.g.*, conjunctival epithelial neoplasms) diseases of the eye.
HAV, HBV, HCV	Hepatitis, hepatocellular carcinoma, lymphoma.
CMV	Hepatitis, retinitis, meningitis.
HSV, VSV	Related mucocutaneous, oropharyngeal and genital diseases, related skin and respiratory infections, varicella-zoster, chicken pox, herpes zoster, post-herpetic neuralgia, conjunctivitis, keratoconjunctivitis, keratitis.
HHV	Exanthem subitum, infectious mononucleosis.
EBV	Infectious mononucleosis, chronic fatigue syndrome, lymphoma, conjunctivitis, keratitis, and related infections of the eye.
Adenoviruses	Upper and lower respiratory tract infections, pneumonia, conjunctivitis.
RSV	Upper and lower respiratory tract infections, pneumonia.
PMV	Mumps and related manifestations, *e.g.*, conjunctivitis.
MV, RV	Measles, Rubella ("German measles") and related manifestations.
Coxsackie viruses	Conjunctivitis, diabetes mellitus, respiratory infections.
Influenza viruses	Upper and lower respiratory tract infections, pneumonia.

HIV, Human Immunodeficiency Virus; HTLV, Human T-cell Lymphocyte Virus; HPV, Human Papilloma Virus; HAV, Hepatitis A Virus; HBV, Hepatitis B Virus; HAV, Hepatitis C Virus; CMV, Cytomegalovirus; HSV, Herpes Simplex Virus (Types I & II); HHV, Human Herpes Virus; EBV, Epstein-Barr Virus; RSV, Respiratory Syncytial Virus; VZV, Varicella-Zoster Virus; PMV, Paramyxovirus; MV, Measles (Rubeola) Virus; RV, Rubella

Table VIII: HIV related infections and diseases treatable using compounds described in this invention	
Organ system	*Viral infection/manifestation or other HIV-associated disease*
Immunologic	AIDS, primary HIV infection.
Dermatological	Anogenital cancers including rectal and cervical cancer, Kaposi's sarcoma, atopic dermatitis, squamous cell carcinoma, hairy leukoplakia, molluscum contagiosum, warts (HPV infections), seborrheic dermatitis, psoriasis, xeroderma, HSV and varicella-zoster infections.
Hematologic	Non-Hodgkin's lymphoma, B cell lymphoma, anemia, neutropenia, thrombocytopenia.
Gastrointestinal	Anorexia, gastroparesis, diarrhea, malabsorption, gastrointestinal CMV infections, esophagitis, colitis, hepatitis, lymphoma.
Ophthalmic	Conjunctivitis, keratitis, keratoconjunctivitis, uveitis, retinitis, chorioretinitis, CMV retinitis, iridocyclitis, vitreitis, choroiditis, papilledema, Kaposi's sarcoma, lymphoma, ocular palsies, conjunctival warts, pre-neoplastic and neoplastic diseases of the eye.
Cardiac	Myocarditis, endocarditis, pericarditis.
Pulmonary	CMV pneumonitis, lymphoid interstitial pneumonitis.
Nephrologic	HIV nephropathy, renal cell carcinoma, amyloidosis, uropathy.
Rheumatologic	Arthralgia, fibromyalgia, Reiter's syndrome, psoriatic arthritis, vasculitis.
Neurologic	Dementia, viral meningitis, viral encephalitis, HIV encephalopathy, progressive multifocal leukoencephalopathy, CNS lymphoma, peripheral and autonomic neuropathies.

Psychiatric	Dysphoric mood disorders, depression, depression associated with chronic diseases and medications, bipolar disorder, anxiety disorders, chronic fatigue syndrome, chronic pain, psychoses, substance abuse disorders and drug addiction.
General	Lymphoma, metastatic lymphoma, Kaposi's sarcoma, wasting syndrome, psychosis.

TABLE IXa: Diseases of the eye treatable using compounds described in this invention	
1. Inflammatory eye diseases associated with viral infections	
Disease	*Virus*
Blepharitis	HSV, VZV, Vaccinia, HPV, molluscum contagiosum
Conjunctivitis	HSV, VZV, EBV, Adenovirus, Vaccinia, Variola, HPV, molluscum contagiosum, influenza
Follicular c.	Newcastle, measles, mumps, rubella, molluscum contagiosum
Hemorrhagic c.	Enterovirus, coxsackie
Catarrhal c	Rubella
Keratitis	HSV, VZV, EBV, Adenovirus, Vaccinia, Variola, HPV, molluscum contagiosum
Keratoconjunctivitis	HSV, VZV, EBV, Adenovirus, Vaccinia, Variola, HPV, molluscum contagiosum
Retinitis	CMV
Uveitis	HPV
Conjunctival warts	HPV
Epithelial neoplasms	HPV
2. Oularplastic diseases	
Benign tumors	Keratocanthoma, molluscum contagiosum, dermoid cysts, neurofibroma, neurofibromatosis, schwannoma (neurilemoma),

	pleiomorphic adenoma
Malignant tumors	Basal cell carcinoma, squamous cell carcinoma, mucoepidermoid carcinoma, melanoma, retinoblastoma, embryonal rhabdomyosarcoma, meningioma, adenoid cystic carcinoma, lymphoid tumors of the orbit, mesenchymal tumors (fibrous hystiocytoma) of the orbit, nasopharyngeal carcinoma.
Vascular lesions	Hemangioma, lymphangioma

TABLE XIb: Ophthalmic diseases treatable using compounds described in this invention (cont'd)	
*Disease Category/Examples of Diseases, Causes or Associated Conditions**	
Conjunctivitis	Acute allergic conjunctivitis (*e.g.* drug-related inflammation, hypersensitivity reactions), chronic (vernal) conjunctivitis, contact lens-associated conjunctivitis, *e.g.* giant papillary conjunctivitis, conjunctival ulceration, including ulceration associated with mucous membrane, conjunctival warts
Blepharitis	Inflammatory etiologies, *e.g.* blepharitis secondary to rosacea
Ophthalmic fibrosis	Steven's-Johnson syndrome with progressive fibrosis and scarring, cicatrization and symblepharon.
Corneal injury	Corneal abrasion or ulceration (*e.g.* contact lens-related injury), or corneal injury of any etiology*.
Dry eye syndrome	See Table below
Pterygium, pinguecula	
Pemphigoid	Includes ophthalmic pemhigori
Scleritis/Episcleritis	
Iridocyclitis	
Endophthalmitis	
Uveal tract diseases	Including glaucoma (primary and secondary etiologies)

	Uveitis, uveoretinitis, panuveitis
Vitreitis, retinitis	*e.g.* congenital retinitis, retinitis pigmentosa
Infectious retinitis	Viral (herpes, cytomegalovirus, HIV), tuberculous, syphititic, fungal (histoplasmosis)
Chorioretinopathies	Chorioretinitis, choroiditis, vitreitis,
Retinopathies	Diabetic retinopathy, hypertensive retinopathy
Maculopathies	Age-related-macular degeneration, white dot syndromes
Cataract	Related to diabetes, age, collagen vascular diseases
Ocular palsies	

*Etiologies of ophthalmic diseases treatable by compounds of this invention include diseases induced or caused by physical agents (*e.g.*, UV radiation), chemical agents (*e.g.*, acids, caustic solvents) immunological etiologies (*e.g.*, collagen vascular diseases, auto-immune, T lymphocyte-related), infectious agents such as viruses (HSV, CMV, HIV), mycoplasma, tuberculosis, syphilis, fungae (histoplasmosis)

TABLE IXc: Ophthalmic diseases treatable using compounds described in this invention (cont'd) - Etiologies of dry eye syndrome

I. Conditions Characterized by Hypofunction of the Lacrimal Gland:

A. Congenital

Familial dysautonomia (Riley-Day syndrome), aplasia of the lacrimal gland (congenital alacrima), trigeminal nerve aplasia, ectodermal dysplasia

B. Acquired

1. Systemic Diseases, *e.g.* Sjögren's Syndrome, progressive systemic sclerosis, sarcoidosis, leukemia, lymphyoma, amyloidosis, hemochromatosis,

2. Infection, *e.g.* mumps

3. Injury, *e.g.* surgical removal of lacrimal gland, irradiation, chemical burn

4. Medications, *e.g.* antihistamines, antimuscarinics (atropine, scopolamine),

general anesthetics (halothane, nitrous oxide), ∃-adrenergic blockers (timolol, practolol), neurogenic, neuroparalytic (facial nerve palsy)
II. Conditions Characterized by Mucin Deficiency
Avitaminosis A, Stevens-Johnson syndrome, ocular pemphigoid, chronic conjuncitivitis (*e.g.* trachoma), chemical burns, drugs and medications
III. Conditions Characterized by Lipid Deficiency
Lid margin scarring, blepharitis
IV. Defective Spreading of Team Film Caused by eyelid abnormalities:
1. Defects, colboma
2. Ectropion or entropion
3. Keratinization of lid margin
4. Decreased or absent blinking secondary to: neurologic disorders, hyperthyroidism, contact lens, drugs and medications, herpes simplex keratitis, leprosy, conjunctival abnormalities, pterygium, symblepharon, proptosis

TABLE IXd: Ophthalmic diseases treatable using compounds described in this invention (cont'd) - Non-hereditary and hereditary degenerative diseases
Macular disorders: Age-related macular degeneration, exudative macular degeneration, atrophic macular degeneration, crystalline retinopathies, retinal toxicosis of systemic medications, idiopathic central serous choroidiopathy, macular edema
Retinovascular diseases and retinopathies: Retinopathy, vasculo-occlusive r., ischemic r., idiopathic r., hypertensive r., proliferative r., diabetic r., vitreoretinopathy, vasculopathies associated with telangiectasias or aneurysms, retinopathies associated with lupus erythematosus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, uveoretinitis or diabetes mellitus, glaucomatous retinopathies

Glaucoma: Primary and secondary open-angle glaucoma, angle-closure glaucoma, glaucoma associated with intraocular inflammation, elevated intraocular pressure associated with acute glaucoma, steroid-induced glaucoma, glaucoma associated with intraocular hemorrhage, pseudoexfoliative syndrome, glaucomatous optic neuropathy and other degenerative changes (*e.g.* retinopathy) associated with glaucoma

Cataract: Age-related (UV radiation) cataract, cataract associated with systemic diseases such as collagen vascular disease, diabetes mellitus, Wilson's disease

Other diseases: Primary or secondary retinal detachment

TABLE IXe: Ophthalmic diseases treatable using compounds described in this invention (cont'd) - Congenital degenerative retinopathies

1. Primary pigmented retinopathies

- Autosomal dominant retinitis pigmentosa, *e.g.* rod-cone and cone-rod degenerations

- Autosomal recessive retinitis pigmentosa, *e.g.* rod-cone and cone-rod degenerations, Lerner's amaurosis congenita

- X-linked recessive pigmented retinopathies, *e.g.* choroideremia

2. Secondary pigmented retinopathies (retinopathies associated with systemic diseases)

- Autosomal dominant pigmented retinopathies, *e.g.* Paget's disease, Charcot-Marie-Tooth, disease, Steinert's disease, Pierre-Marie syndrome

- Autosomal recessive pigmented retinopathies, *e.g.* diabetes mellitus, mannosidoses, mucopolysccharidoses, Batten's d., Refsum's d., Usher syndrome

- X-linked recessive pigmented retinopathies, *e.g.* Hunter syndrome

TABLE X: Diseases or conditions treatable using compounds described in this invention
I. Promote healing in the following clinical situations:
Surgical or traumatic wounds to healthy tissues or organs
Wounds caused by chemical or physical agents, *e.g.* ulcers caused by caustic or erosive chemicals, pressure sores
Wounds associated with disease states, *e.g.* diabetic ulcers, venous stasis ulcers
Wounds in diseased tissues or organs
II. Promote cell survival and prevent apoptosis in neurodegenerative diseases:
Alzheimer's disease
Parkinson's disease
Amyotrophic lateral sclerosis
Spinal cord ischemia, spinal cord injury secondary to trauma or disease
III. Attenuation or arrest of the following conditions or processes:
Time-dependent aging of cells and tissues
Aging induced by chemical or physical agents, *e.g.* sun-induced skin aging
Accelerated aging associated with diseases, *e.g.* Werner's syndrome
IV. Vitalization and revitalization of organs and tissues
Promoting cell growth and preventing cell death in the aging process
Promoting therapeutic or non-pathological angiogenesis as a therapeutic approach to treating diseases such as congestive heart failure and cardiomyopathy
Promoting growth of organs and tissues for repair or transplantation

[00103] The compounds of the instant invention are further useful to suppress the mediators of neurogenic inflammation (*e.g.*, substance P or the tachykinins), and may be used in the treatment of rheumatoid arthritis, psoriasis, topical inflammation such as is associated with sunburn, eczema, or other sources of itching; and allergies,

including asthma. The compounds can also function as neuromodulators in the central nervous system, with useful applications in the treatment of Alzheimer's disease and other forms of dementia, pain (as a spinal analgesic), and headaches. Furthermore, in disorders involving myocardial fibrosis, myocardial ischemia, pathological conditions secondary to the autoimmune response to allograft transplantation, the splanchnic blood flow, including hepatic fibrosis, cirrhosis and esophageal varices, the compounds of the invention can provide cytoprotection.

4.6 Modes of Administration

[00104] The compounds of Formulae I or II and/or pharmaceutical compositions thereof may be advantageously used in human medicine. As previously described, compounds of Formulae I or II and/or pharmaceutical compositions thereof are useful for the treatment or prevention of various diseases listed in Section 4.5.

[00105] When used to treat or prevent the above diseases or disorders, compounds and/or pharmaceutical compositions thereof may be administered or applied singly, or in combination with other agents. The compounds and/or pharmaceutical compositions thereof may also be administered or applied singly, in combination with other pharmaceutically active agents including other compounds of Formulae I or II.

[00106] The current invention provides methods of treatment and prophylaxis by administration to a patient in need of such treatment of a therapeutically effective amount of a compound and/or pharmaceutical composition thereof. The patient may be an animal, more preferably, is a mammal and most preferably, is a human.

[00107] The present compounds and/or pharmaceutical compositions thereof, which comprise one or more compounds of Formulae I and/or II, are preferably administered orally. The compounds and/or pharmaceutical compositions of the invention may also be administered by any other convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, *etc.*). Administration can be systemic or local. Various delivery systems are known, (*e.g.*, encapsulation in liposomes, microparticles, microcapsules, capsules, *etc.*) that can be used to administer a compound and/or pharmaceutical composition of the invention. Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual,

intranasal, intracerebral, intravaginal, transdermal, rectally, by inhalation, or topically, particularly to the ears, nose, eyes, or skin. The preferred mode of administration is left to the discretion of the practitioner and will depend in-part upon the site of the medical condition. In most instances, administration will result in the release of the compounds and/or pharmaceutical compositions of the invention into the bloodstream.

[00108] In specific embodiments, it may be desirable to administer one or more compounds and/or pharmaceutical composition of the invention locally to the area in need of treatment. This may be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. In one embodiment, administration can be by direct injection at the site (or former site) of the disease.

[00109] In certain embodiments, it may be desirable to introduce one or more compounds and/or pharmaceutical compositions of the invention into the central nervous system by any suitable route, including intraventricular, intrathecal and epidural injection. Intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

[00110] A compound and/or pharmaceutical composition of the invention may also be administered directly to the lung by inhalation. For administration by inhalation, a compound and/or pharmaceutical composition of the invention may be conveniently delivered to the lung by a number of different devices. For example, a Metered Dose Inhaler ("MDI"), which utilizes canisters that contain a suitable low boiling propellant, (*e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or any other suitable gas) may be used to deliver compounds of the invention directly to the lung.

[00111] Alternatively, a Dry Powder Inhaler ("DPI") device may be used to administer a compound and/or pharmaceutical composition of the invention to the lung. DPI devices typically use a mechanism such as a burst of gas to create a cloud of dry powder inside a container, which may then be inhaled by the patient. DPI devices are also well known in the art. A popular variation is the multiple dose DPI ("MDDPI") system, which allows for the delivery of more than one therapeutic dose.

MDDPI devices are available from companies such as AstraZeneca, GlaxoWellcome, IVAX, Schering Plough, SkyePharma and Vectura. For example, capsules and cartridges of gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch for these systems.

[00112] Another type of device that may be used to deliver a compound and/or pharmaceutical composition of the invention to the lung is a liquid spray device supplied, for example, by Aradigm Corporation, Hayward, CA. Liquid spray systems use extremely small nozzle holes to aerosolize liquid drug formulations that may then be directly inhaled into the lung.

[00113] In one embodiment, a nebulizer is used to deliver a compound and/or pharmaceutical composition of the invention to the lung. Nebulizers create aerosols from liquid drug formulations by using, for example, ultrasonic energy to form fine particles that may be readily inhaled (see *e.g.*, Verschoyle *et al.*, *British J. Cancer*, **1999**, 80, Suppl. 2, 96, which is herein incorporated by reference). Examples of nebulizers include devices supplied by Batelle Pulmonary Therapeutics, Columbus OH (Armer *et al.*, United States Patent No. 5,954,047; van der Linden *et al.*, United States Patent No. 5,950,619; van der Linden *et al.*, United States Patent No. 5,970,974).

[00114] In another embodiment, an electrohydrodynamic ("EHD") aerosol device is used to deliver a compound and/or pharmaceutical composition of the invention to the lung. EHD aerosol devices use electrical energy to aerosolize liquid drug solutions or suspensions (*e.g.*, Noakes *et al.*, United States Patent No. 4,765,539). The electrochemical properties of the formulation may be important parameters to optimize when delivering a compound and/or pharmaceutical composition of the invention to the lung with an EHD aerosol device and such optimization is routinely performed by one of skill in the art. EHD aerosol devices may more efficiently deliver drugs to the lung than existing pulmonary delivery technologies.

[00115] In another embodiment, the compounds and/or pharmaceutical compositions thereof can be delivered in a vesicle, in particular a liposome (Langer, *Science*, **1990**, 249:1527-1533; Treat *et al.*, in "Liposomes in the Therapy of Infectious Disease and Cancer," Lopez-Berestein and Fidler (eds.), Liss, New York, pp.353-365 (1989))

[00116] In another embodiment, the compounds and/or pharmaceutical compositions thereof can be delivered *via* sustained release systems, preferably oral sustained release systems. In one embodiment, a pump may be used (Langer, *supra*; Sefton, *CRC Crit Ref Biomed Eng.* **1987**, 14:201; Saudek *et al.*, *N. Engl. J Med.* **1989**, 321:574).

[00117] In another embodiment, polymeric materials can be used (Medical Applications of Controlled Release," Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); "Controlled Drug Bioavailability," Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Langer *et al.*, *J Macromol. Sci. Rev. Macromol Chem.* **1983**, 23:61; Levy *et al.*, *Science* **1985**, 228: 190; During *et al.*, *Ann. Neurol.* **1989**, 25:351; Howard *et al.*, *J. Neurosurg.* **1989**, 71:105). In another embodiment, polymeric materials are used for oral sustained release delivery. Preferred polymers include sodium carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and hydroxyethylcellulose (most preferred, hydroxypropyl methylcellulose). Other preferred cellulose ethers have been described (Alderman, *Int. J. Pharm. Tech. & Prod. Mfr.*, **1984**, 5(3) 1-9). Factors affecting drug release are well known to the skilled artisan and have been described in the art (Bamba *et al.*, *Int. J. Pharm.*, **1979**, 2, 307).

[00118] In another embodiment, enteric-coated preparations can be used for oral sustained release administration. Preferred coating materials include polymers with a pH-dependent solubility (*i.e.*, pH-controlled release), polymers with a slow or pH-dependent rate of swelling, dissolution or erosion (*i.e.*, time-controlled release), polymers that are degraded by enzymes (*i.e.*, enzyme-controlled release) and polymers that form firm layers that are destroyed by an increase in pressure (*i.e.*, pressure-controlled release).

[00119] In still another embodiment, osmotic delivery systems are used for oral sustained release administration (Verma *et al.*, *Drug Dev. Ind. Pharm.*, **2000**, 26:695-708). In another embodiment, OROS™ osmotic devices are used for oral sustained release delivery devices (Theeuwes *et al.*, United States Patent No. 3,845,770; Theeuwes *et al.*, United States Patent No. 3,916,899).

[00120] In yet another embodiment, a controlled-release system can be placed in proximity of the target of the compounds and/or pharmaceutical composition of the invention, thus requiring only a fraction of the systemic dose (See, *e.g.*, Goodson, in "Medical Applications of Controlled Release," *supra* vol. 2, pp. 115-138 (1984)).

Other controlled-release systems discussed in Langer, **1990**, *Science* 249:1527-1533 may also be used.

4.7 Pharmaceutical Compositions

[00121] The present pharmaceutical compositions contain a therapeutically effective amount of one or more compounds of Formulae I and/or II, preferably in purified form, together with a suitable amount of a pharmaceutically acceptable vehicle, so as to provide a form for proper administration to a patient. When administered to a patient, the compounds and pharmaceutically acceptable vehicles are preferably sterile. Water is a preferred vehicle when a compound is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid vehicles, particularly for injectable solutions. Suitable pharmaceutical vehicles also include excipients such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present pharmaceutical compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents may be used.

[00122] Pharmaceutical compositions comprising a compound of Formulae I or II may be manufactured by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Pharmaceutical compositions may be formulated in conventional manner using one or more physiologically acceptable carriers, diluents, excipients or auxiliaries, which facilitate processing of compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

[00123] The present pharmaceutical compositions can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment, the pharmaceutically acceptable vehicle is a capsule (see *e.g.*, Grosswald *et al.*, United States Patent No. 5,698,155). Other examples of suitable pharmaceutical vehicles

have been described in the art (Remington, "The Science and Practice of Pharmacy," Philadelphia College of Pharmacy and Science, 20th Edition, 2000).

[00124] For topical administration a compound may be formulated as applicator sticks, solutions, suspensions, gels, creams, ointments, pastes, jellies, paints, powders, aerosols solutions, *etc.* as is well-known in the art.

[00125] Systemic formulations include those designed for administration by injection, *e.g.*, subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal, oral or pulmonary administration. Systemic formulations may be made in combination with a further active agent that improves mucociliary clearance of airway mucus or reduces mucous viscosity. These active agents include, but are not limited to, sodium channel blockers, antibiotics, N-acetyl cysteine, homocysteine and phospholipids.

[00126] In one embodiment, compounds are formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compounds for intravenous administration are solutions in sterile isotonic aqueous buffer. For injection, a compound may be formulated in aqueous solutions, preferably, in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. The solution may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. When necessary, the pharmaceutical compositions may also include a solubilizing agent. Pharmaceutical compositions for intravenous administration may optionally include a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. When a compound is administered by infusion, it can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. When a compound is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[00127] For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[00128] Pharmaceutical compositions for oral delivery may be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Orally administered pharmaceutical compositions may contain one or more optionally agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry coloring agents and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or pill form, the compositions may be coated to delay disintegration and absorption in the gastrointestinal tract, thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compounds of the invention. In these later platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time delay material such as glycerol monostearate or glycerol stearate may also be used. Oral compositions can include standard vehicles such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, *etc.* Such vehicles are preferably of pharmaceutical grade.

[00129] For oral liquid preparations such as, for example, suspensions, elixirs and solutions, suitable carriers, excipients or diluents include water, saline, alkyleneglycols (*e.g.*, propylene glycol), polyalkylene glycols (*e.g.*, polyethylene glycol) oils, alcohols, slightly acidic buffers between pH 4 and pH 6 (*e.g.*, acetate, citrate, ascorbate at between about 5.0 mM to about 50.0 mM) *etc.* Additionally, flavoring agents, preservatives, coloring agents, bile salts, acylcarnitines and the like may be added.

[00130] For buccal administration, the pharmaceutical compositions may take the form of tablets, lozenges, *etc.* formulated in conventional manner.

[00131] Liquid drug formulations suitable for use with nebulizers and liquid spray devices and EHD aerosol devices will typically include a compound with a pharmaceutically acceptable vehicle. Preferably, the pharmaceutically acceptable vehicle is a liquid such as alcohol, water, polyethylene glycol or a perfluorocarbon. Optionally, another material may be added to alter the aerosol properties of the solution or suspension of compounds of the invention. Preferably, this material is

liquid such as an alcohol, glycol, polyglycol or a fatty acid. Other methods of formulating liquid drug solutions or suspension suitable for use in aerosol devices are known to those of skill in the art (*e.g.*, Biesalski, United States Patent Nos. 5,112,598 and 5,556,611).

[00132] A compound may also be formulated in rectal or vaginal pharmaceutical compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

[00133] For ocular administration, a compound may be formulated as a solution, emulsion, suspension, *etc.* suitable for administration to the eye. A variety of vehicles suitable for administering compounds to the eye are known in the art. Specific non-limiting examples are described in United States Patent No. 6,261,547; United States Patent No. 6,197,934; United States Patent No. 6,056,950; United States Patent No. 5,800,807; United States Patent No. 5,776,445; United States Patent No. 5,698,219; United States Patent No. 5,521,222; United States Patent No. 5,403,841; United States Patent No. 5,077,033; United States Patent No. 4,882,150; and United States Patent No. 4,738,851.

[00134] In addition to the formulations described previously, a compound may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, a compound may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[00135] When a compound is acidic, it may be included in any of the above-described formulations as the free acid, a pharmaceutically acceptable salt, a solvate or a hydrate. Pharmaceutically acceptable salts substantially retain the activity of the free acid, may be prepared by reaction with bases and tend to be more soluble in aqueous and other protic solvents than the corresponding free acid form.

4.8 Doses

[00136] The present methods for treatment or prevention of the various diseases listed in Tables (I-X), *supra*, require administration of a compound of Formulae I or II, or a pharmaceutical composition thereof, to a patient in need of such treatment or prevention.

[00137] The amount of a compound that will be effective in the treatment or prevention of the various diseases listed in Tables (I-X), *supra*, in a patient will depend on the specific nature of the condition and can be determined by standard clinical techniques known in the art. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The amount of a compound administered will, of course, be dependent on, among other factors, the subject being treated, the weight of the subject, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

[00138] Preferably, the dosage forms are adapted to be administered to a patient no more than twice per day, more preferably, only once per day. Dosing may be provided alone or in combination with other drugs and may continue as long as required for effective treatment or prevention of the various diseases listed in Tables (I-X), *supra*.

[00139] Suitable dosage ranges for oral administration are dependent on the potency of the particular compound but are generally about 0.1 mg to about 200 mg of drug per kilogram body weight, more preferably about 1 to about 100mg of drug per kilogram body weight per day. Dosage ranges for topical treatment are between about 0.1% to about 0.5% (weight /volume) in a gel, cream or ointment. A typical dose for intra-dermal or intraocular injection is between 0.25 to about 10 mg depending the portion of eye that is being treated. Dosage ranges for other forms of administration may be readily determined by methods known to the skilled artisan.

4.9 Combination Therapy

[00140] In certain embodiments, a compound of Formula I or II and/or pharmaceutical compositions thereof can be used in combination therapy with at least one other therapeutic agent which may be a different compound of Formula I or II and/or pharmaceutical compositions thereof. The compound and/or pharmaceutical composition thereof and the other therapeutic agent can act additively or, more preferably, synergistically. In one embodiment, a compound and/or a pharmaceutical composition thereof is administered concurrently with the administration of another therapeutic agent. In another embodiment, a compound and/or pharmaceutical composition thereof is administered prior or subsequent to administration of another therapeutic agent.

[00141] Examples of other therapeutic agents which can be used with compounds of Formulae I and II include, but are not limited to, diabetes mellitus-treating agents, diabetic complication-treating agents, antihyperlipemic agents, hypotensive or antihypertensive agents, anti-obesity agents, diuretics, chemotherapeutic agents, immunotherapeutic agents immunosuppressive agents, and the like.

[00142] Examples of agents for treating diabetes mellitus include insulin formulations (*e.g.*, animal insulin formulations extracted from a pancreas of a cattle or a swine; a human insulin formulation synthesized by a gene engineering technology using microorganisms or methods), insulin sensitivity enhancing agents, pharmaceutically acceptable salts, hydrates, or solvates thereof (*e.g.*, pioglitazone, troglitazone, rosiglitazone, netoglitazone, balaglitazone, rivoglitazone, tesaglitazar, farglitazar, CLX-0921, R-483, NIP-221, NIP-223, DRF-2189, GW-7282TAK-559, T-131, RG-12525, LY-510929, LY-519818, BMS-298585, DRF-2725, GW-1536, GI-262570, KRP-297, TZD18 (Merck), DRF-2655, and the like), alpha-glycosidase inhibitors (*e.g.*, voglibose, acarbose, miglitol, emiglitate and the like), biguanides (*e.g.*, phenformin, metformin, buformin and the like)or sulfonylureas (*e.g.*, tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride and the like) as well as other insulin secretion-promoting agents (*e.g.*, repaglinide, senaglinide, nateglinide, mitiglinide, GLP-1 and the like), amyrin agonist (*e.g.*, pramlintide and the like), phosphotyrosinphosphatase inhibitor (*e.g.*, vanadic acid and the like) and the like.

[00143] Examples of agents for treating diabetic complications include, but are not limited to, aldose reductase inhibitors (*e.g.*, tolrestat, epalrestat, zenarestat, zopolrestat, minalrestat, fidareatat, SK-860, CT-112 and the like), neurotrophic factors (*e.g.*, NGF, NT-3, BDNF and the like), PKC inhibitors (*e.g.*, LY-333531 and the like), advanced glycation end-product (AGE) inhibitors (*e.g.*, ALT946, pimagedine, pyradoxamine, phenacylthiazolium bromide (ALT766) and the like), active oxygen quenching agents (*e.g.*, thioctic acid or derivative thereof, a bioflavonoid including flavones, isoflavones, flavonones, procyanidins, anthocyanidins, pycnogenol, lutein, lycopene, vitamins E, coenzymes Q, and the like), cerebrovascular dilating agents (*e.g.*, tiapride, mexiletene and the like).

[00144] Antihyperlipemic agents include, for example, statin-based compounds which are cholesterol synthesis inhibitors (*e.g.*, pravastatin, simvastatin, lovastatin,

atorvastatin, fluvastatin, rosuvastatin and the like), squalene synthetase inhibitors or fibrate compounds having a triglyceride-lowering effect (*e.g.*, fenofibrate, gemfibrozil, bezafibrate, clofibrate, sinfibrate, clinofibrate and the like).

[00145] Hypotensive agents include, for example, angiotensin converting enzyme inhibitors (*e.g.*, captopril, enalapril, delapril, benazepril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril and the like) or angiotensin II antagonists (*e.g.*, losartan, candesartan cilexetil, olmesartan medoxomil, eprosartan, valsartan, telmisartan, irbesartan, tasosartan, pomisartan, ripisartan forasartan, and the like).

[00146] Antiobesity agents include, for example, central antiobesity agents (*e.g.*, dexfenfluramine, fenfluramine, phentermine, sibutramine, amfepramone, dexamphetamine, mazindol, phenylpropanolamine, clobenzorex and the like), gastrointestinal lipase inhibitors (*e.g.*, orlistat and the like), β-3 agonists (*e.g.*, CL-316243, SR-58611-A, UL-TG-307, SB-226552, AJ-9677, BMS-196085 and the like), peptide-based appetite-suppressing agents (*e.g.*, leptin, CNTF and the like), cholecystokinin agonists (*e.g.*, lintitript, FPL-15849 and the like) and the like.

[00147] Diuretics include, for example, xanthine derivatives (*e.g.*, theobromine sodium salicylate, theobromine calcium salicylate and the like), thiazide formulations (*e.g.*, ethiazide, cyclopenthiazide, trichloromethiazide, hydrochlorothiazide, hydroflumethiazide, bentylhydrochlorothiazide, penflutizide, polythiazide, methyclothiazide and the like), anti-aldosterone formulations (*e.g.*, spironolactone, triamterene and the like), decarboxylase inhibitors (*e.g.*, acetazolamide and the like), a chlorbenzenesulfonamide formulations (*e.g.*, chlorthalidone, mefruside, indapamide and the like), azosemide, isosorbide, ethacrynic acid, piretanide, bumetanide, furosemide and the like.

[00148] Chemotherapeutic agents include, for example, alkylating agents (*e.g.*, cyclophosphamide, iphosphamide and the like), metabolism antagonists (*e.g.*, methotrexate, 5-fluorouracil and the like), anticancer antibiotics (*e.g.*, mitomycin, adriamycin and the like), vegetable-derived anticancer agents (*e.g.*, vincristine, vindesine, taxol and the like), cisplatin, carboplatin, etoposide and the like. Among these substances, 5-fluorouracil derivatives such as furtulon and neofurtulon are preferred.

[00149] Immunotherapeutic agents include, for example, microorganisms or bacterial components (*e.g.*, muramyl dipeptide derivative, picibanil and the like),

polysaccharides having immune potentiating activity (*e.g.*, lentinan, sizofilan, krestin and the like), cytokines obtained by a gene engineering technology (*e.g.*, interferon, interleukin (IL) and the like), colony stimulating factors (*e.g.*, granulocyte colony stimulating factor, erythropoetin and the like) and the like, among these substances, those preferred are IL-1, IL-2, IL-12 and the like.

[00150] Immunosuppressive agents include, for example, calcineurin inhibitor/immunophilin modulators such as cyclosporine (Sandimmune, Gengraf, Neoral), tacrolimus (Prograf, FK506), ASM 981, sirolimus (RAPA, rapamycin, Rapamune), or its derivative SDZ-RAD, glucocorticoids (prednisone, prednisolone, methylprednisolone, dexamethasone and the like), purine synthesis inhibitors (mycophenolate mofetil, MMF, CellCept(R), azathioprine, cyclophosphamide), interleukin antagonists (basiliximab, daclizumab, deoxyspergualin), lymphocyte-depleting agents such as antithymocyte globulin (Thymoglobulin, Lymphoglobuline), anti-CD3 antibody (OKT3), and the like.

[00151] In addition, agents whose cachexia improving effect has been established in an animal model or at a clinical stage, such as cyclooxygenase inhibitors (*e.g.*, indomethacin and the like) [Cancer Research, Vol.49, page 5935-5939, 1989], progesterone derivatives (*e.g.*, megestrol acetate) [Journal of Clinical Oncology, Vol.12, page 213-225, 1994], glucosteroid (*e.g.*, dexamethasone and the like), metoclopramide-based agents, tetrahydrocannabinol-based agents, lipid metabolism improving agents (*e.g.*, eicosapentanoic acid and the like) [British Journal of Cancer, Vol.68, page 314-318, 1993], growth hormones, IGF-1, antibodies against TNF-.alpha., LIF, IL-6 and oncostatin M may also be employed concomitantly with a compound according to the present invention.

[00152] The preferred combinations of the agents for the prevention and/or treatment of diabetes are, a compound according to the current invention and:

1) an insulin formulation and a biguanide;

2) a sulfonylurea agent and a biguanide;

3) a sulfonylurea agent and an alpha-glycosidase inhibitor;

4) a biguanide and an alpha-glycosidase inhibitor;

5) a blood sugar reducing agent and other kind of agents for treating diabetic complications;

6) an 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor;

7) any other two kinds of agents mentioned above;

8) an agent that inhibits activity of angiotensin converting enzyme;

9) an anti-dyslipidemic fibrate.

[00153] The preferred combinations of the agents for the prevention and/or treatment of diabetes are, a compound according to the current invention and:

1) an insulin formulation and a biguanide;

2) a sulfonylurea agent and a biguanide;

3) a sulfonylurea agent and an alpha-glycosidase inhibitor;

4) a biguanide and an alpha-glycosidase inhibitor;

5) a blood sugar reducing agent and the other kind of agents for treating diabetic complications;

6) an 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor;

7) any other two kinds of agents mentioned above;

8) an agent that inhibits activity of angiotensin converting enzyme;

9) an anti-dyslipidemic fibrate.

[00154] In case that a compound or the composition of the present invention is used in combination with the other agent, an amount of each other agent can be reduced in a range which is safe in light of its adverse effect. Especially, an insulin sensitivity enhancing agent, a biguanide and a sulfonylurea agent can be used at a lower dose than those usually used so that adverse effects which may be caused by these agents can be safely avoided. In addition, an agent for treating diabetic complications, an anti-hyperlipemic agent and a hypotensive agent can also be used at a lower dose, so that adverse effect which may be caused by them can be avoided effectively.

[00155] Administering both an angiotensin receptor blocker and a compound of the present invention formulated together in a single pill or tablet, may be used to treat glucose intolerance or type 2 diabetes and other PPAR responsive disorders without causing fluid retention, edema, or congestive heart failure. For this purpose, a pharmaceutical composition comprising: (i) a compound of the present invention in a therapeutically effective amount sufficient to prophylactically prevent, slow, delay or treat a metabolic, inflammatory, atopic, autoimmune, proliferative, or cardiovascular disorder in humans; (ii) an angiotensin II type 1 receptor antagonist in a therapeutically effective amount sufficient to prevent, slow, delay, or treat fluid

retention, peripheral edema, pulmonary edema, or congestive heart failure; and (iii) a pharmaceutically acceptable vehicle may be formulated. The angiotensin II type 1 receptor antagonist may be a compound selected from the group consisting of telmisartan, irbesartan, valsartan, losartan, candesartan, candesartan cilexetil, olmesartan, olmesartan medoximil, losartan, valsartan, eprosartan, irbesartan, tasosartan, pomisartan, ripisartan, and forasartan, or an analog thereof, or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof.

[00156] It should also be noted the compounds of the present invention may be administered with a thiazolidinedione selected from the group consisting of pioglitazone, troglitazone, rosiglitazone, netoglitazone, balaglitazone, rivoglitazone, CLX-0921, R-483, NIP-221, NIP-223, DRF-2189, and the like, or an analog thereof, or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof to treat or prevent various disorders listed in Tables (I-X), *supra*. Alternatively, the compounds of the present invention may be administered with a non-thiazolidinedione selected from the group of compounds consisting of tesaglitazar, farglitazar, ragaglitazar, LY818, T131, LSN862, DRF 4832, LM 4156, LY 510929, LY 519818, TY 51501, X 334, GW-7282, TAK-559, T-131, RG-12525, BMS-298585, DRF-2725, GW-1536, GI-262570, KRP-297, TZD18 (Merck), DRF-2655, or an analog thereof, or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof. Other thiazolidinedione or non-thiazolidinedione activators of PPARs that are familiar to those skilled in the art can also be employed in combination with the compound of the invention to treat or prevent various disorders listed in Tables (I-X), *supra*.

[00157] The compounds of this invention can also be given orally in combination with natural or synthetic compounds that bind to or modify the activity of the vitamin D receptor or other nuclear hormone receptor or in combination with compounds that bind to or modify the activity of the retinoid X receptor to provide for a synergistic effect in the treatment or prevention of the disorders listed in Table I-X, *supra*. Examples of such compounds include, but are not limited to, vitamin D analogs, various retinoic acid derivatives, and other ligands for retinoid X receptors or retinoic acid receptors including but not limited to compounds such as LG100268, tazarotene, TTNPB, AGN 190121, adapalene or LGD1069 (Targretin).

[00158] Synergistic therapeutic effects can be achieved by oral or topical administration of the compounds of the current invention together with orally, topically or intravenously administered drugs that bind to and modify the activity of either the vitamin D receptor, the glucocorticoid receptor, the intracellular enzyme calcineurin, the retinoid X receptors, the retinoic acid receptors, or other PPARs such as PPARα or PPARδ. Examples of effective retinoids are 9-cis-retinoic acid, 13-cis-retinoic acid, all-trans-retinoic acid (at-RA). Preferred retinoids for this purpose would include 13-cis-retinoic acid, tazarotene, or Targretin. Examples of effective vitamin D analogs are 1,25-dihydroxy-vitamin D, calcipotriene and calcipotriol.

[00159] Synergistic therapeutic effects can be achieved by oral or topical administration of the compounds of the current invention together with orally, topically or intravenously administered natural or synthetic antioxidants. These include, but are not limited to, ascorbic acid and its derivatives (*e.g.*, vitamin C), the tocopherols (*e.g.*, vitamin E, vitamin E succinate), carotenes and carotenoids (*e.g.*, ß-carotene), alpha-lipoic acid, probucols, flavones, isoflavones and flavonols (*e.g.*, quercetin, genistein, catechin, apigenin, lutein, luteolin), lycopene, pycnogenol, glutathione and its derivatives (*e.g.*, N-acetylcysteine and dithiothreitol), and phytoestrogens and phenolic anthocyanidin and procyanidin derivatives (*e.g.*, resveratrol, cyanidin, cinnamic acid).

4.10 Assays

[00160] The compounds of the current invention may be tested for their ability to activate PPARγ isoforms by utilizing standard screening methods known to those skilled in the art including, but not limited to, cell based transactivation assays or cell free assays that test the ability of a compound to activate PPARγ construct by measuring the output of a reporter signal that reflects the extent of the PPAR activation. For example, a compound of the current invention is added to the culture media of CV1 cells or other cells that can be transfected with a full length or partial PPARγ cDNA sequence together with a reporter construct containing a PPAR response element or other appropriate response element fused to a reporter gene such as luciferase. The ability of a compound of the current invention to activate PPARγ is tested by measuring the luciferase reporter gene activity. Any compound found to

activate PPARγ according to these or other methods can be used to treat disorders known to be responsive to PPAR activators.

[00161] PPARγ activators that have improved safety profile and decreased risk for causing fluid retention, edema, or congestive heart failure may be identified by testing their ability to inhibit angiotensin converting enzyme activity or their ability to block the angiotensin receptor. PPARγ ligands or PPARγ activators that also inhibit ACE activity or block angiotensin II type 1 receptors represent an improvement over existing PPAR ligands for treating PPAR responsive disorders because they have reduced likelihood of causing fluid retention, edema, or congestive heart failure. A variety of assays are available that can be used by those skilled in the art to determine whether a PPARγ activator can also block the angiotensin II type 1 receptor or inhibit the activity of angiotensin converting enzyme.

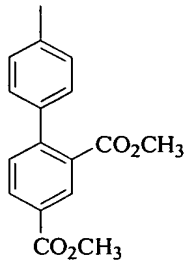
5. Examples

[00162] The invention is further defined by reference to the following examples. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

5.1 Example 1:

Suzuki coupling of 4-tolylboronic acid with dimethyl 4-bromobenzene-1,3-dioate:

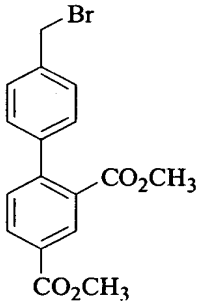
[00163] To a round bottom flask equipped with a magnetic stir bar, heating mantle, and reflux condenser was added bromo compound, dimethyl (4'-methylphenyl)benzene-1,3-dioate, (1mmol), 4-tolylboronic acid (1.1mmol), toluene (21mL), 2N sodium carbonate solution (6mL), methanol 3(mL) and tetrakistriphenyl phosphine (5 %mol). The resulting mixture was vigorously refluxed until TLC showed disappearance of bromophenyl derivative (~2h). After completion of the reaction, the reaction mixture was cooled, neutralized with 2N HCl and extracted with EtOAc. The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under vacuum, purification by column chromatography afforded the biphenyl derivative, dimethyl (4'-methylphenyl)benzene-1,3-dioate (yield 91%).



^{1}HNMR ($CDCl_3$, 400MHz): δ 2.40 (s, 3H); 3.71 (s, 3H); 3.95 (s, 3H); 7.22 (s, 4H); 7.45 (d, 1H); 8.16 (d, 1H); 8.46 (s, 1H)

5.2 Example 2: Bromination with NBS

[00164] A solution of dimethyl (4'-methylphenyl)benzene-1,3-dioate (10mmol), N-bromosuccinamide (12mmol) and benzoylperoxide (0.1mmol) in carbon tetrachloride (25mL) was refluxed for 3h. After cooling, the mixture was filtered, and the filtrate was concentrated under vacuum to give a residue, dimethyl (4'-bromomethyl)benzene-1,3-dioate, that was purified by column chromatography (yield 85%).

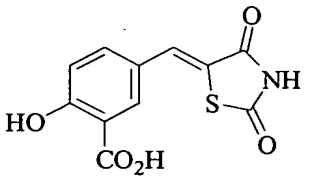


^{1}HNMR ($CDCl_3$,400MHz): δ 3.47 (s, 2H); 3.66 (s, 3H); 3.95 (s, 3H); 7.26 (d, 2H); 7.35 (d, 2H); 7.46 (d, 1H); 8.16 (dd, 1H); 8.46 (d, 1H).

5.3 Example 3: Preparation of (Z)-5-((2,4-dioxothiazolidin-5-ylidene)methyl)-2-hydroxybenzoic acid

[00165] A mixture of the 5-formyl-2-hydroxybenzoic acid (6.64g, 40mmol), 2,4-thiazolidinedione (4.68g, 40mmol), piperidine (0.085g, 1mmol) and acetic acid (0.06g, 1mmol) in toluene (40mL) was heated under reflux with azeotropic removal of water for 12h. The mixture was cooled to 5°C. Filtration gave a pale orange solid,

2-hydroxy-5-((Z)-(2,4-dioxothiazolidin-5-ylidene)methyl)benzoic acid, which was washed with cold toluene and dried (9.22g, yield 87%).

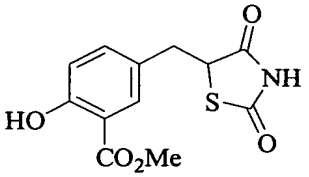


^{1}HNMR (400MHz, $CDCl_3$): δ 6.90 (d, 1H); 7.56 (d, 1H); 7.69 (s, 1H); 7.96 (s, 1H); 8.46 (bs, 1H); 12.4 (bs, 1H).

5.4 Example 4:

Preparation of methyl 2-hydroxy-5-((2,4-dioxothiazolidin-5-yl)methyl)benzoate:

[00166] A solution of enone, (2-hydroxy-5-((Z)-(2,4-dioxothiazolidin-5-ylidene)methyl)benzoic acid, (2.65g, 10mmol) in 1M aq NaOH (20mL) was adjusted to pH 9.1 by addition of 1M aq. HCl, was successively treated with a solution of chloro(pyridine)bis(dimethylglyoximato)cobalt(III) (40mg, 0.1mmol) in water (1mL) and sodium borohydride (0.25g, 6.5mmol) and stirred at 30°C. After 2h, the reaction mixture was cooled to 20-25°C, and (the pH of the reaction mixture) adjusted to 2.0 by addition of 1M aq. HCl. After extraction with EtOAc, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude acid was converted to methyl ester, methyl 2-hydroxy-5-((2,4-dioxothiazolidin-5-yl)methyl)benzoate, by dissolving in anhydrous methanol (20mL) with catalytic conc. H_2SO_4 (2.1g, 74% two steps).



^{1}HNMR ($CDCl_3$, 400MHz): δ 3.11 (dd, 1H); 3.43 (dd, 1H); 3.95 (s, 3H); 4.51 (dd, 1H); 6.95 (d, 1H); 7.32 (d, 1H); 7.70 (s, 1H); 8.78 (bs, 1H); 10.73 (s, 1H).

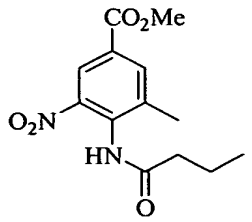
5.5 Example 5:

Preparation of methyl 7-methyl-2-propyl-3H-benzo[d]imidazole-5-carboxylate:

[00167] Methyl 4-amino-3-methyl-5-nitrobenzoate (10 mmol) was acylated with butyryl chloride (10 mmol) in chlorobenzene at 100°C. After completion of the reaction the reaction mixture was washed with saturated sodium bicarbonate and

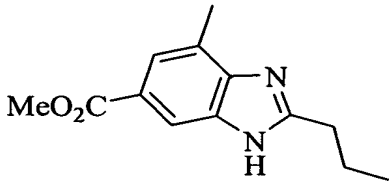
extracted with chlorobenzene. The resulting amide was reacted with fuming nitric acid in sulfuric acid at 0°C. The resulting nitro-amide was reduced with hydrogen (30 psi) and palladium (5%) on charcoal in methanol. After completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was evaporated *in vacuo* (yield 54%).

Methyl 4-(butyramido)-3-methyl-5-nitrobenzoate:



^{1}HNMR ($CDCl_3$, 400MHz,): δ 1.02 (t, 3H); 1.79 (m, 2H); 2.30 (s, 3H); 2.43 (t, 2H); 3.90 (s, 3H); 5.72 (bs, 1H); 8.12 (s, 1H); 8.47 (s, 1H)

[00168] The crude product, methyl 3-amino-4-(butyramido)-5-methylbenzoate, was dissolved in glacial acetic acid (20mL) and heated to reflux for 2h. After evaporation, water (50mL) was added, the pH was adjusted to 8 by addition of concentrated ammonia, and the mixture was extracted with ethyl acetate. The combined extracts were dried, the solvent was evaporated, and the residue was purified by column chromatography gave methyl 7-methyl-2-propyl-3H-benzo[d]imidazole-5-carboxylate (yield 88%).



^{1}HNMR ($CDCl_3$, 400MHz,): δ 0.97 (t, 3H); 1.88 (m, 2H); 2.58 (s, 3H); 2.94 (t, 2H); 3.93 (s, 3H); 7.78 (s, 1H); 8.12 (s, 1H)

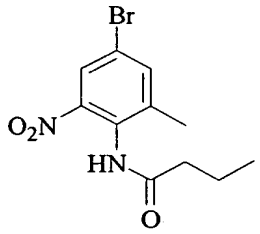
5.6 Example 6:

Preparation of 6-bromo-4-methyl-2-propyl-1H-benzo[d]imidazole:

[00169] 4-Bromo-2-methyl-6-nitrobenzenamine (10 mmol) was acylated with butyryl chloride (10 mmol) in chlorobenzene at 100°C. After completion of the

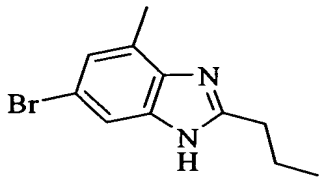
reaction the reaction mixture was washed with saturated sodium bicarbonate and extracted with chlorobenzene. The resulting amide was reacted with fuming nitric acid in sulfuric acid at 0°C. The resulting nitro-amide was reduced with hydrogen (30 psi) and palladium (5%) on charcoal in methanol. After completion of the reaction, the reaction mixture was filtered through Celite, and the filtrate was evaporated *in vacuo* (yield 65%).

N-(4-bromo-2-methyl-6-nitrophenyl)butyramide:



^{1}HNMR ($CDCl_3$, 400MHz,): δ 0.90 (t, 3H); 1.64 (m, 2H); 2.22 (s, 3H); 2.45 (t, 2H); 7.75 (s, 1H); 8.06 (s, 1H)

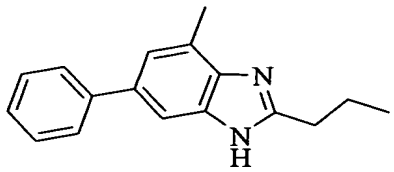
[00170] The crude product, N-(2-amino-4-bromo-6-methylphenyl)butyramide, was dissolved in glacial acetic acid (20mL) and heated to reflux for 2h. After evaporation, water (50mL) was added, the pH was adjusted to 8 by addition of concentrated ammonia, and the mixture was extracted with ethyl acetate. The combined extracts were dried, the solvent was evaporated, and the residue was purified by column chromatography gave 6-Bromo-4-methyl-2-propyl-1H-benzo[d]imidazole (yield 76%).



^{1}HNMR($CDCl_3$, 400MHz,): δ 0.97 (t, 3H); 1.86 (m, 2H); 2.52 (s, 3H); 3.07 (t, 2H); 7.34 (m, 5H); 7.39 (d, 1H); 7.49 (s, 1H)

5.7 Example 7:
Preparation of 4-methyl-6-phenyl-2-propyl-1H-benzo[d]imidazole:

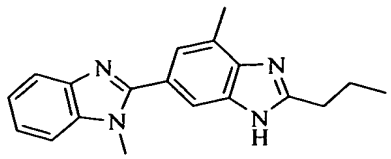
[00171] To a round bottom flask equipped with a magnetic stir bar, heating mantle, and reflux condenser was added 6-Bromo-4-methyl-2-propyl-1H-benzo[d]imidazole (example 6) (1mmol), phenylboronic acid (1.1mmol), toluene (21mL), 2N sodium carbonate solution (6mL), methanol 3(mL) and tetrakistriphenyl phosphine (5 %mol). The resulting mixture was vigorously refluxed until TLC showed disappearance of 6-Bromo-4-methyl-2-propyl-1H-benzo[d]imidazole (~3h). After completion of the reaction, the reaction mixture was cooled, neutralized with 2N HCl and extracted with EtOAc. The combined organic layers were washed with water, brine and dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under vacuum, purification by column chromatography afforded the biphenyl derivative, 4-methyl-6-phenyl-2-propyl-1H-benzo[d]imidazole (yield 91%).



^{1}HNMR($CDCl_3$, 400MHz,): δ 0.92 (t, 3H); 1.90 (m, 2H); 2.64 (s, 3H); 3.07 (t, 2H); 7.34 (m, 5H); 7.39 (d, 1H); 7.49 (s, 1H).

5.8 Example 8:
Preparation of 4-methyl-6-(1-methyl-1*H*-benzo[d]imidazol-2-yl)-2-propyl-1*H*-benzo[d]imidazole

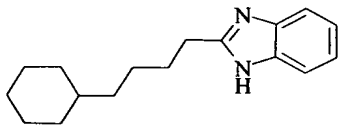
[00172] The methyl ester, methyl 7-methyl-2-propyl-3H-benzo[d]imidazole-5-carboxylate (example 5) (1mmol), N^1-methylbenzene-1,2-diamine (1mmol) and polyphosphoric acid (5mL) were mixed together and heated to 150°C. After 10h the reaction mixture was diluted with water (20mL) and the pH was adjusted to 8 by addition of concentrated ammonia, and the mixture was extracted with ethyl acetate. The combined extracts were dried, the solvent was evaporated, and the residue was purified by column chromatography gave 4-Methyl-6-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-propyl-1*H*-benzo[*d*]imidazole(yield 45%).



^{1}HNMR($CDCl_3$, 400MHz,): δ 0.95 (t,3H); 1.8 (m, 2H); 2.55 (s, 3H); 2.81 (t,2H); 3.87 (s, 3H); 7.43 (m, 4H); 7.52 (s,1H); 7.82 (m, 1H).

5.9 Example 9:
Preparation of 2-(4-cyclohexylbutyl)-1H-benzo[d]imidazole

[00173] The 5-cyclohexylpentanoic acid (1mmol), phenylenediamine (1mmol) and polyphosphoric acid (5mL) was mixed together and heated to 150°C. After 10h the reaction mixture was diluted with water (20mL) and the pH was adjusted to 8 by addition of concentrated ammonia, and the mixture was extracted with ethyl acetate. The combined extracts were dried, the solvent was evaporated, and the residue was purified by column chromatography gave 2-(4-cyclohexylbutyl)-1H-benzo[d]imidazole (yield 65%).

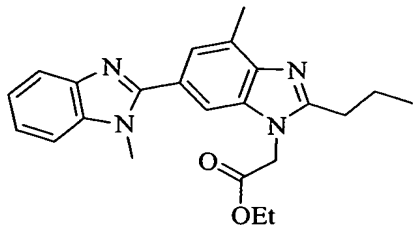


^{1}HNMR($CDCl_3$, 400MHz,): δ 0.82 (m, 2H); 1.15 (m, 6H); 1.36 (m, 2H); 1.62 (m, 5H); 1.83 (m, 2H); 2.92 (t, 2H); 7.21 (dd, 2H), 7.54 (dd, 2H).

5.10 Example 10:
N-alkylation of 4-methyl-6-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-propyl-1H-benzo[d]-imidazole:

[00174] To a 60% dispersion of NaH (48mg, 1.2 mmol) in anhydrous THF (10mL) was added a solution of 4-methyl-6-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-propyl-1H-benzo[d]-imidazole (1mmol) in THF (10mL) at 0°C. After stirring for 30min at 0°C, the ethyl bromo acetate (1.2mmol) was added, and stirring was continued until completion of the reaction. The reaction was quenched with saturated ammonium chloride and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and purified by column chromatography to give

ethyl 2-(4-methyl-6-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-propyl-1H-benzo[d]-imidazol-1-yl)acetate (yield 92%).

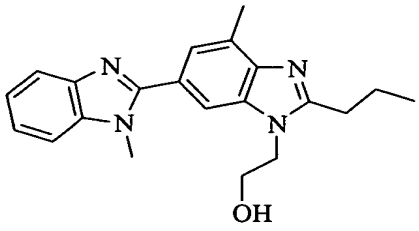


^{1}HNMR (400MHz, $CDCl_3$): 1.05 (t, 3H); 1.21 (t, 3H); 1.85 (m, 2H); 2.70 (s, 3H); 2.87 (t, 2H); 3.83 (s, 3H); 4.21 (q, 2H); 4.87 (s, 2H); 7.46 (m, 4H); 7.52 (s, 1H); 7.80 (m, 1H).

5.11 Example 11

Reduction of ethyl 2-(4-methyl-6-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-propyl-*1H*-benzo[*d*]-imidazol-1-yl)acetate:

[00175] To a solution of ethyl 2-(4-methyl-6-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-propyl-1H-benzo[d]-imidazol-1-yl)acetate (1mmol) in anhydrous THF (20mL) lithium aluminium hydride (38mg, 1mmol) was added at 0°C. After 30 min, the reaction mixture was quenched with saturated sodium sulphate (2mL) and stirring continued for an additional 30min. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to give a residue, 2-(4-methyl-6-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-propyl-1H-benzo[d]imidazol-1-yl)ethanol, that was purified by column chromatography (yield 95%).



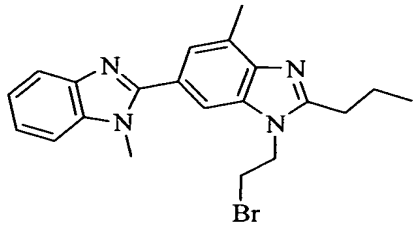
^{1}HNMR ($CDCl_3$, 400MHz,): δ 1.02 (t, 3H); 1.81 (m, 2H); 2.68 (S, 3H); 2.81 (t, 2H); 3.48 (s, 3H); 3.78 (bs, 2H); 4.18 (bs, 2H); 7.32 (m, 5H); 7.82 (m, 1H).

5.12 Example 12:

Preparation of 2-(1-(2-bromoethyl)-4-methyl-2-propyl-1H-benzo[d]imidazol-6-yl)-1-methyl-1H-benzo[d]imidazole:

[00176] A 50ml round bottom flask was charged with 2-(4-methyl-6-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-propyl-1H-benzo[d]imidazol-1-yl)ethanol (1mmol),

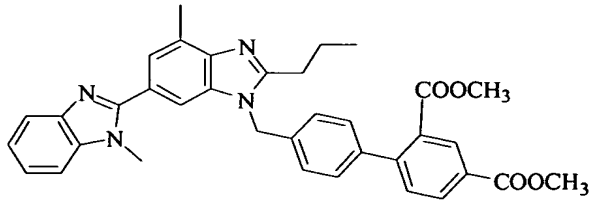
CBr_4 (.4g, 1.2mmol), and CH_2Cl_2 (20 mL) and cooled to 0 °C. Over the course of 5 min, PPh_3 (0.32g, 1.2mmol) was added in portions. The reaction was allowed to reflux for 2 h. After completion of the reaction, the solvent was removed by rotary evaporation, and the crude reaction mixture was purified by column chromatography, yielding 1-(2-bromoethyl)-4-methyl-6-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-propyl-1H-benzo[d]imidazole (yield 58%).



^{1}HNMR ($CDCl_3$, 400MHz,): δ 1.06 (t, 3H); 1.89 (m, 2H); 2.70 (s, 3H); 2.90 (t, 2H) 3.62 (t, 2H); 3.80 (s, 3H); 4.96 (t, 2H); 7.29 (m, 4H); 7.55 (s, 1H); 7.80 (d, 1H).

5.13 Example 13:
Preparation of Pro-averysartan

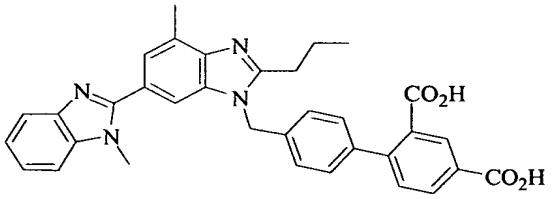
[00177] To a solution of 4-methyl-6-(1-methyl-1*H*-benzo[d]imidazol-2-yl)-2-propyl-1*H*-benzo[d]imidazole , as prepared in Example 8, (1 mmol) in DMF (5 ml) was added anhydrous cesium carbonate (0.72g, 2mmol) and dimethyl (4'-bromomethyl)benzene-1,3-dioate as in example 2 (1.2 mmol) in DMF (5 ml) at 60 °C. After 5h, water was added, and the crude product was extracted with EtOAc, washed with brine, dried over MgSO4, and concentrated *in vacuo*. The residue, purified by column chromatography on silica gel gave proaverysartan (yield 35%).



^{1}HNMR ($CDCl_3$, 400MHz,): δ 1.04 (t, 3H); 1.85 (m, 2H); 2.76 (s, 3H); 2.91 (t, 2H); 3.60 (s, 3H); 3.77 (s, 3H), 3.92 (s, 3H); 5.43 (s, 2H); 7.09 (d, 2H); 7.27 (m, 6H); 7.43 (d, 2H); 7.77 (m, 1H); 8.13 (d, 1H); 8.46 (s, 1H).

5.14 Example 14:
Preparation of Averysartan

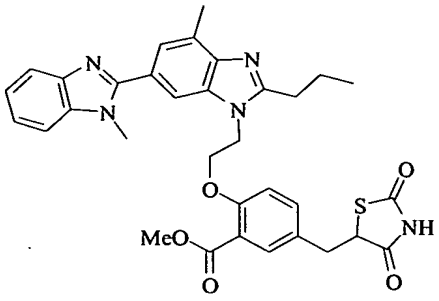
[00178] The ester, proaverysartan, (1.81 mmol) was dissolved in THF (10 mL) and water (2.5 mL) was added. To this mixture was added LiOH (0.062 g, 2.59 mmol) in water (1 mL), and the mixture was left overnight at RT. THF was removed by rotary evaporation, and conc HCl (0.25 mL) was added. The layers were separated, and the aq. layer was extracted with ethylacetate (25 mL). The organic layer was washed with water and dried over $MgSO_4$ and concentrated to give the acid, averysartan (yield 85%).



^{1}HNMR (MeOH-d_4,400 MHz): δ 1.06 (t, 3H); 1.82 (m, 2H); 2.73 (s, 3H); 3.06 (t, 2H); 3.82 (s, 3H); 5.64 (s, 2H); 7.20 (d, 2H); 7.43 (m, 6H); 7.60 (m, 2H); 7.74 (d, 1H); 8.10 (d, 1H); 8.35 (s, 1H).

5.15 Example 15:
Preparation of Methyl 5-((2,4-dioxothiazolidin-5-yl)methyl)-2-(2-(4-methyl-6-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-propyl-1H-benzo[d]imidazol-1-yl)ethoxy)benzoate

[00179] To a solution of methyl 5-((2,4-dioxothiazolidin-5-yl)methyl)-2-hydroxybenzoate, as prepared in Example 4, (1 mmol) in DMF (5 ml) was added anhydrous cesium carbonate (0.72g, 2mmol) and 2-(1-(2-bromoethyl)-4-methyl-2-propyl-1H-benzo[d]imidazol-6-yl)-1-methyl-1H-benzo[d]imidazole as prepared in example 12 (1.2 mmol) in DMF (5 ml) at 60 °C. After 5h, water was added, and the crude product was extracted with EtOAc, washed with brine, dried over MgSO4, and concentrated *in vacuo*. The residue, purified by column chromatography on silica gel gave methyl 5-((2,4-dioxothiazolidin-5-yl)methyl)-2-(2-(4-methyl-6-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-propyl-1H-benzo[d]imidazol-1-yl)ethoxy)benzoate (yield 55%).

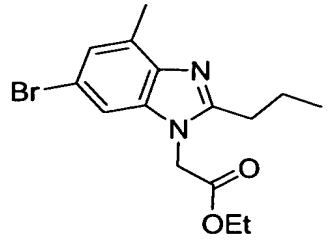


^{1}HNMR ($CDCl_3$, 400MHz,): δ 1.14 (t, 3H); 1.98 (m, 2H); 2.74 (s, 3H); 2.80 (dd, 1H); 2.94 (m, 2H); 3.33 (dd, 1H); 3.86 (s, 3H); 3.95 (s, 3H); 3.98 (m, 2H); 4.35 (m, 2H); 4.56 (m, H); 7.51 (s, 1H); 7.61 (d, 2H); 7.83 (d, 1H).

5.16 Example 16:

N-alkylation of 6-bromo-4-methyl-2-propyl-1H-benzo[d]imidazole

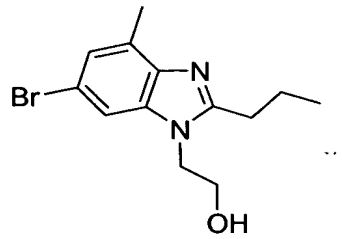
[00180] To a 60% dispersion of NaH (48mg, 1.2 mmol) in anhydrous THF (10mL) was added a solution of 6-bromo-4-methyl-2-propyl-1H-benzo[d]imidazole (1mmol) in THF (10mL) at 0°C. After stirring for 30min at 0°C, the ethyl bromo acetate (1.2mmol) was added, and stirring was continued until completion of the reaction. The reaction was quenched with saturated ammonium chloride and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and purified by column chromatography to give ethyl 2-(6-bromo-4-methyl-2-propyl-1H-benzo[d]imidazol-1-yl)acetate (yield 95%).



^{1}HNMR($CDCl_3$, 400MHz,): δ 1.04 (t, 3H); 1.26 (t, 3H); 1.85 (m, 2H); 2.61 (s, 3H); 2.80 (t, 2H); 4.23 (s, 2H); 4.74 (s, 2H); 7.17 (bs, 2H)

5.17 Example 17:
Reduction of ethyl 2-(6-bromo-4-methyl-2-propyl-1H-benzo[d]imidazol-1-yl)acetate

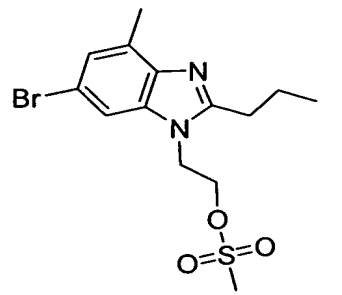
[00181] To a solution of ethyl 2-(6-bromo-4-methyl-2-propyl-1H-benzo[d]imidazol-1-yl)acetate (1mmol) in anhydrous THF (20mL) lithium aluminium hydride (38mg, 1mmol) was added at 0°C. After 30 min, the reaction mixture was quenched with saturated sodium sulphate (2mL) and stirring continued for an additional 30min. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to give a residue, 2-(6-Bromo-4-methyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethanol, that was purified by column chromatography(yield 95%).



^{1}HNMR ($CDCl_3$, 400MHz,): δ 0.98 (t, 3H); 1.72 (m, 2H); 2.39 (s, 3H); 2.83 (t, 2H); 4.01 (t, 2H); 4.15 (t, 2H); 6.99 (s, 1H); 7.22 (s, 1H).

5.18 Example 18:
Preparation of 2-(6-bromo-4-methyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethyl methanesulfonate

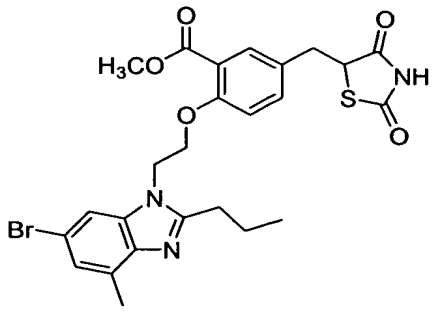
[00182] To a solution of 2-(6-Bromo-4-methyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethanol (10mmol) in CH_2Cl_2 (15 ml) was added NEt_3 (2.0 ml, 14.41mmol) and MsCl (1.1 ml, 14.41 mmol) at 0°C. After stirring for 2 h at room temperature, the reaction mixture was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give 2-(6-bromo-4-methyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethyl methanesulfonate as colorless oil (yield 83%).



^{1}HNMR ($CDCl_3$, 400MHz,): δ 1.08 (t, 3H); 1.88 (m, 2H); 2.61 (s, 3H); 2.81 (s, 3H); 2.87 (t, 2H); 4.41 (t, 2H); 4.48 (t, 2H); 7.18 (s, 1H); 7.30 (s, 1H).

5.19 Example 19:
Methyl 2-(2-(6-bromo-4-methyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethoxy)-5-((2,4-dioxothiazolidin-5-yl)methyl)benzoate

[00183] To a solution of methyl 5-((2,4-dioxothiazolidin-5-yl)methyl)-2-hydroxybenzoate, as prepared in Example 4, (1 mmol) in DMF (5 ml) was added anhydrous cesium carbonate (0.72g, 2mmol) and 2-(6-bromo-4-methyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethyl methanesulfonate as prepared in example 18 (1.2 mmol) in DMF (5 ml) at 60 °C. After 5h, water was added, and the crude product was extracted with EtOAc, washed with brine, dried over MgSO4, and concentrated *in vacuo*. The residue, purified by column chromatography on silica gel gave methyl 2-(2-(6-bromo-4-methyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethoxy)-5-((2,4-dioxothiazolidin-5-yl)methyl)benzoate (yield 45%).

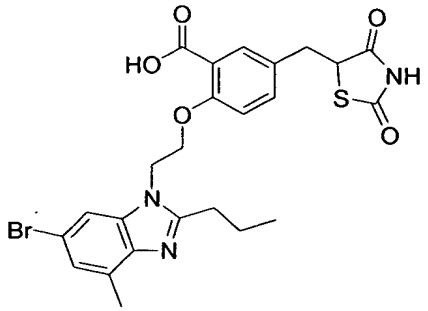


^{1}HNMR ($CDCl_3$, 400MHz,): δ 0.99 (t, 3H); 1.80 (m, 2H), 2.45 (s, 3H); 2.87 (t, 2H); 3.06 (dd, 1H); 3.26 (dd, 1H); 3.68 (s, 3H); 4.31 (bs, 2H); 4.55 (bs, 2H); 4.85 (dd, 1H); 7.05 (d, 2H); 7.09 (s, 1H); 7.33 (d, 1H); 7.44 (s, 1H); 7.64 (s, 1H).

5.20 Example 20:
Preparation of 2-(2-(6-Bromo-4-methyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethoxy)-5-((2,4-dioxothiazolidin-5-yl)methyl)benzoic acid

[00184] The ester, methyl 2-(2-(6-bromo-4-methyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethoxy)-5-((2,4-dioxothiazolidin-5-yl)methyl)benzoate as prepared in example 19, (1.81 mmol) was dissolved in THF (10 mL) and water (2.5 mL) was added. To this mixture was added LiOH (0.062 g, 2.59 mmol) in water (1 mL), and the mixture was left overnight at RT. THF was removed by rotary evaporation, and conc HCl (0.25 mL) was added. The layers were separated, and the

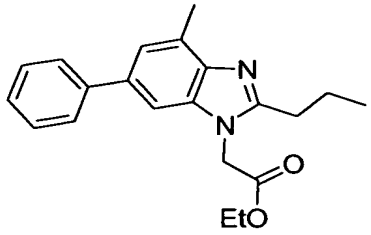
aq. layer was extracted with ethylacetate (25 mL). The organic layer was washed with water and dried over $MgSO_4$ and concentrated to give the acid, 2-(2-(6-Bromo-4-methyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethoxy)-5-((2,4-dioxothiazolidin-5-yl)methyl)benzoic acid (yield 89%).



^{1}HNMR (MeOH-d_4, 400MHz,): δ 1.10 (t, 3H); 1.78 (m, 2H), 2.43 (s, 3H); 2.93 (t, 2H); 3.16 (dd, 1H); 3.36 (dd, 1H); 4.43 (bs, 2H); 4.65 (bs, 2H); 4.89 (dd; 1H); 7.09 (d, 2H); 7.30 (s, 1H); 7.32 (d, 1H); 7.48 (s, 1H); 7.76 (s, 1H).

5.21 Example 21:
N-alkylation of 4-methyl-6-phenyl-2-propyl-1H-benzo[d]imidazole

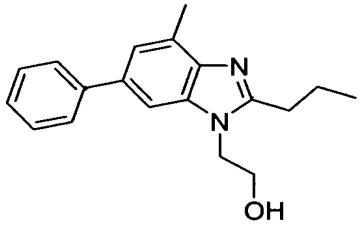
[00185] To a 60% dispersion of NaH (48mg, 1.2 mmol) in anhydrous THF (10mL) was added a solution of 4-methyl-6-phenyl-2-propyl-1H-benzo[d]imidazole (1mmol) in THF (10mL) at 0°C. After stirring for 30min at 0°C, the ethyl bromo acetate (1.2mmol) was added, and stirring was continued until completion of the reaction. The reaction was quenched with saturated ammonium chloride and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and purified by column chromatography to give ethyl 2-(4-methyl-6-phenyl-2-propyl-1H-benzo[d]imidazol-1-yl)acetate (yield 90%).



^{1}HNMR($CDCl_3$, 400MHz,): δ 1.09 (t, 3H); 1.29 (t, 3H); 1.91 (m, 2H); 2.74 (s, 3H); 2.89 (t, 2H); 4.25 (q, 2H); 4.87 (s, 2H), 7.23 (s, 1H); 7.33 (t, 2H); 7.46 (t, 2H); 7.63 (d, 2H)

5.22 Example 22:
Reduction of ethyl 2-(4-methyl-6-phenyl-2-propyl-1H-benzo[d]imidazol-1-yl)acetate

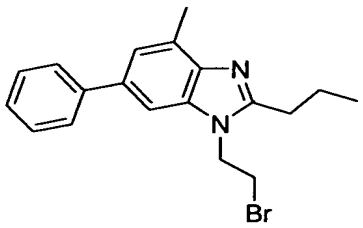
[00186] To a solution of ethyl 2-(4-methyl-6-phenyl-2-propyl-1H-benzo[d]imidazol-1-yl)acetate (1mmol) in anhydrous THF (20mL) lithium aluminium hydride (38mg, 1mmol) was added at 0°C. After 30 min, the reaction mixture was quenched with saturated sodium sulphate (2mL) and stirring continued for an additional 30min. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to give a residue, 2-(4-methyl-6-phenyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethanol, that was purified by column chromatograph (yield 97%).



^{1}HNMR ($CDCl_3$, 400MHz,): δ 0.97 (t, 3H); 1.71 (m, 2H); 2.39 (s, 3H); 2.87 (t, 2H); 4.07 (bs, 2H); 4.24 (bs, 2H); 7.05 (s, 1H); 7.26 (s, 1H); 7.35 (t, 1H); 7.44 (t, 2H); 7.59 (d, 2H).

5.23 Example 23:
Preparation of Bromide

[00187] A 50ml round bottom flask was charged with 2-(4-Methyl-6-phenyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethanol (1 mmol), CBr_4 (.4g, 1.2mmol), and CH_2Cl_2 (20 mL) and cooled to 0 °C. Over the course of 5 min, PPh_3 (0.32g, 1.2mmol) was added in portions. The reaction was allowed to reflux for 2 h. After completion of the reaction, the solvent was removed by rotary evaporation, and the crude reaction mixture was purified by column chromatography, yielding 1-(2-bromoethyl)-4-methyl-6-phenyl-2-propyl-1H-benzo[d]imidazole (yield 75%).

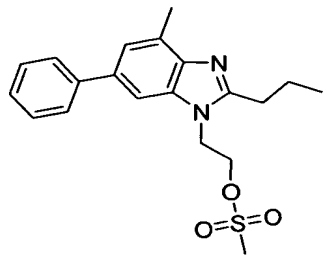


^{1}HNMR ($CDCl_3$, 400MHz,): δ 1.08 (t, 3H; 1.89 (m, 2H); 2.70 (s, 3H); 3.01 (t, 2H); 3.85 (t, 2H); 4.51 (t, 2H); 7.34 (m, 3H); 7.43 (t, 2H); 7.61 (d, 2H)

5.24 Example 24:

Preparation of 2-(4-methyl-6-phenyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethyl methanesulfonate

[00188] To a solution of 2-(4-methyl-6-phenyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethanol (10mmol) in CH_2Cl_2 (15 ml) was added NEt_3 (2.0 ml, 14.41mmol) and MsCl (1.1 ml, 14.41 mmol) at 0°C. After stirring for 2 h at room temperature, the reaction mixture was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give 2-(4-methyl-6-phenyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethyl methanesulfonate as colorless oil (yield 98%).

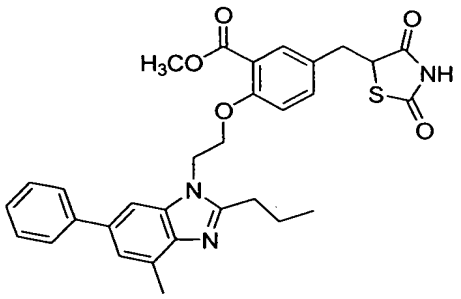


^{1}HNMR ($CDCl_3$, 400MHz,): δ 1.10 (t, 3H); 1.93 (m, 2H); 2.73 (s, 3H); 2.77 (s, 3H); 2.95 (t, 2H); 4.54 (bs, 4H); 7.35 (m, 3H); 7.46 (t, 2H); 7.65 (d, 2H).

5.25 Example 25:

Preparation of Methyl 5-((2,4-dioxothiazolidin-5-yl)methyl)-2-(2-(4-methyl-6-phenyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethoxy)benzoate

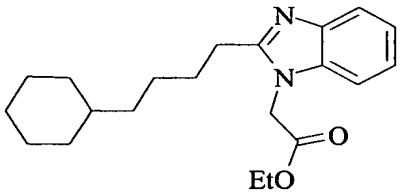
[00189] To a solution of methyl 5-((2,4-dioxothiazolidin-5-yl)methyl)-2-hydroxybenzoate, as prepared in Example 4, (1 mmol) in DMF (5 ml) was added anhydrous cesium carbonate (0.72g, 2mmol) and 2-(4-methyl-6-phenyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethyl methanesulfonate as prepared in example in 24 (1.2 mmol) in DMF (5 ml) at 60 °C. After 5h, water was added, and the crude product was extracted with EtOAc, washed with brine, dried over MgSO4, and concentrated *in vacuo*. The residue, purified by column chromatography on silica gel gave methyl 5-((2,4-dioxothiazolidin-5-yl)methyl)-2-(2-(4-methyl-6-phenyl-2-propyl-1H-benzo[d]imidazol-1-yl)ethoxy) benzoate (yield 65%).



^{1}HNMR ($CDCl_3$, 400MHz,): δ 1.02 (t, 3H); 1.82 (m, 2H); 2.54 (s, 3H); 2.92 (t, 2H); 3.07 (dd, 1H); 3.27 (dd, 1H); 3.62 (s, 3H); 4.38 (bs, 2H); 4.62 (bs, 2H); 4.85 (dd, 1H); 7.08 (d, 1H); 7.26 (s, 1H); 7.31 (dd, 2H); 7.43 (m, 3H); 7.64 (s, 1H); 7.70 (d, 2H).

5.26 Example 26:
N-alkylation of 2-(4-cyclohexylbutyl)-1H-benzo[d]imidazole

[00190] To a 60% dispersion of NaH (48mg, 1.2 mmol) in anhydrous THF (10mL) was added a solution of 2-(4-cyclohexylbutyl)-1H-benzo[d]imidazole as prepared in example 9 (1mmol) in THF (10mL) at 0°C. After stirring for 30min at 0°C, the ethyl bromo acetate (1.2mmol) was added, and stirring was continued until completion of the reaction. The reaction was quenched with saturated ammonium chloride and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and purified by column chromatography to give ethyl 2-(2-(4-cyclohexylbutyl)-1H-benzo[d]imidazol-1-yl)acetate (yield 96%).

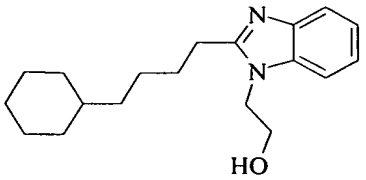


^{1}HNMR($CDCl_3$, 400MHz,): δ 0.87 (m, 2H); 1.21 (m, 9H); 1.46 (m, 2H); 1.72 (m, 5H); 1.90 (m, 2H); 2.83 (t, 2H); 4.25 (q, 2H); 4.83 (s, 2H); 7.25 (m, 3H); 7.45 (d, 1H).

5.27 Example 27:
Reduction of ethyl 2-(2-(4-cyclohexylbutyl)-1H-benzo[d]imidazol-1-yl)acetate:

[00191] To a solution of ethyl 2-(2-(4-cyclohexylbutyl)-1H-benzo[d]imidazol-1-yl)acetate (1mmol) in anhydrous THF (20mL) lithium aluminium hydride (38mg, 1mmol) was added at 0°C. After 30 min, the reaction mixture was quenched with saturated sodium sulphate (2mL) and stirring continued for an additional 30min. The

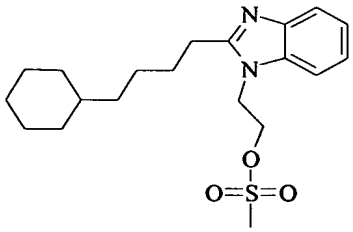
reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to give a residue, 2-(2-(4-Cyclohexylbutyl)-1H-benzo[d]imidazol-1-yl)ethanol, that was purified by column chromatography (yield 90%).



^{1}HNMR ($CDCl_3$, 400MHz,): δ 0.86 (m, 2H); 1.16 (m, 5H); 1.26 (m, 3H), 1.55 (m, 2H); 1.68 (m, 5H); 2.54 (t, 2H); 4.04 (t, 2H); 4.19 (t, 2H); 7.09 (t, 1H); 7.14 (t, 1H); 7.25 (d, 1H); 7.40 (d, 1H).

5.28 Example 28: Preparation of 2-(2-(4-Cyclohexylbutyl)-1H-benzo[d]imidazol-1-yl)ethyl methanesulfonate

[00192] To a solution of 2-(2-(4-Cyclohexylbutyl)-1H-benzo[d]imidazol-1-yl)ethanol (10mmol) in CH_2Cl_2 (15 ml) was added NEt_3 (2.0 ml, 14.41mmol) and MsCl (1.1 ml, 14.41 mmol) at 0°C. After stirring for 2 h at room temperature, the reaction mixture was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give 2-(2-(4-Cyclohexylbutyl)-1H-benzo[d]imidazol-1-yl)ethyl methanesulfonate as colorless oil (yield 98%).

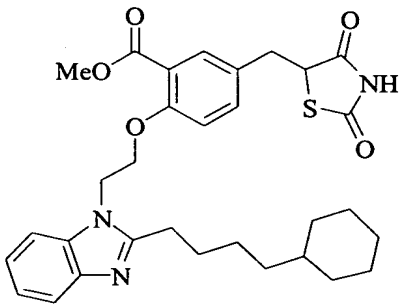


^{1}HNMR ($CDCl_3$, 400MHz,): δ 0.81 (m, 2H); 1.13 (m, 5H); 1.40 (m, 2H); 1.62 (m, 5H); 1.82 (m, 2H); 2.60 (s, 3H); 2.80 (t, 2H); 4.36 (bs, 4H); 7.18 (m, 2H); 7.23 (d, 1H); 7.66 (d, 1H).

5.29 Example 29:

Preparation of Methyl 2-(2-(2-(4-cyclohexylbutyl)-1H-benzo[d]imidazol-1-yl)ethoxy)-5-((2,4-dioxothiazolidin-5-yl)methyl)benzoate

[00193] To a solution of methyl 5-((2,4-dioxothiazolidin-5-yl)methyl)-2-hydroxybenzoate, as prepared in Example 4, (1 mmol) in DMF (5 ml) was added anhydrous cesium carbonate (0.72g, 2mmol) and 2-(2-(4-Cyclohexylbutyl)-1H-benzo[d]imidazol-1-yl)ethyl methanesulfonate as prepared in Example 28 (1.2 mmol) in DMF (5 ml) at 60 °C. After 5h, water was added, and the crude product was extracted with EtOAc, washed with brine, dried over MgSO4, and concentrated *in vacuo*. The residue, purified by column chromatography on silica gel gave methyl 2-(2-(2-(4-cyclohexylbutyl)-1H-benzo[d]imidazol-1-yl)ethoxy)-5-((2,4-dioxothiazolidin-5-yl)methyl)benzoate (yield 43%).



^{1}HNMR ($CDCl_3$, 400MHz,): δ 0.87 (m, 2H); 1.21 (m, 5H); 1.46 (m, 2H); 1.67 (m, 5H); 1.83 (m, 2H); 3.0 (t, 2H); 3.07 (dd, 1H); 3.42 (dd, 1H); 3.82 (s, 3H); 4.32 (t, 2H); 4.43 (dd, 1H); 4.58 (t, 2H); 6.72 (d, 1H); 7.23 (m, 3H); 7.38 (m, 1H); 7.63 (bs, 1H); 7.77 (dd, 1H).

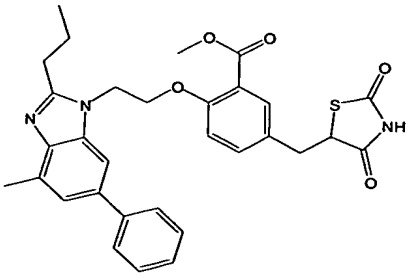
5.30 Example 30:

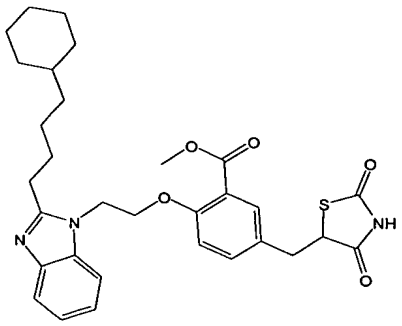
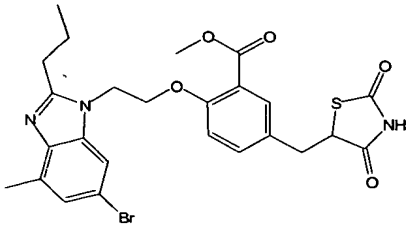
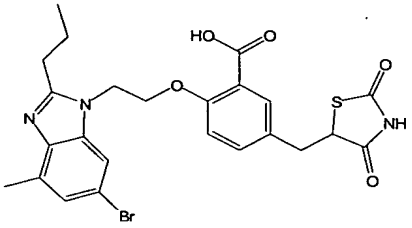
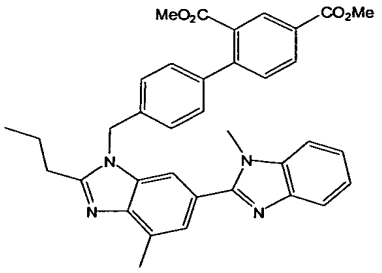
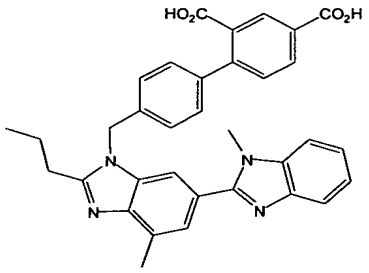
Determination of PPARγ Activity

[00194] PPARγ activity was determined by transactivation assays in CV-1 cells (CCL-70 line from American Type Culture Collection (ATCC), Bethesda, Maryland) transfected using the GenePorter transfection reagent (Gene Therapy Systems, San Diego, California) to deliver 200 ng of a PPARγ expression plasmid and 1 μg of a luciferase reporter plasmid and 400 ng pCMVSport b-gal (Gibco, Grand Island, New Jersey) as an internal control. 24 hr post-transfection, cells were treated with varying concentrations of the test compounds of this invention, and incubated for an

additional 24 hr. Rosiglitazone and pioglitazone, a known PPARγ full agonist, and telmisartan, a known ARB and PPARγ partial agonist (Benson et al. Hypertension (2004) in press) are used as controls. Cell extracts were assayed for luciferase and ß-galactosidase activity using Promega (Madison, Wisconsin) assay systems. All treatments were performed in triplicate, and normalized for β-galactosidase activity. Agonist concentrations yielding half maximal activation (EC50 values) were calculated using GraphPad Prism version 3.03 (GraphPad Software, Inc., San Diego, California).

[00195] Telmisartan significantly activated PPARγ (5-8 fold) when tested at concentrations (1 - 5 mM) that can be achieved in plasma with conventional oral dosing (Stangier J, et al. J Int Med Res (2000) 28:149-67). Telmisartan functioned as a moderately potent (EC50 = 4.5 mM), PPARγ agonist, activating the receptor to 25% - 30% of the maximum level of activity achieved by the full agonists pioglitazone and rosiglitazone. Irbesartan activated PPARγ (2-3 fold activation) when tested at 10 mM. None of the other ARBs tested caused any significant activation of PPAR even when tested at higher concentrations (more than 10 mM). These experiments demonstrate that two known ARBs, telmisartan and irbesartan, are also activators of PPARγ. Because PPARγ activators can be used to treat and prevent type 2 diabetes, the metabolic syndrome, and other clinical disorders responsive to treatment with PPAR activators, these experiments demonstrate the utility of telmisartan and irbesartan for the prevention and treatment of type 2 diabetes, the metabolic syndrome, and other disorders known to be responsive to treatment with PPAR activators.

Structure	**Mol.Form (M. Wt.)**	**PPAR-γ Fold activation**
	$C_{31}H_{31}N_3O_5S$ (557.66)	7.4x @ 10 uM 6.1x @ 1 uM 1.2x @ 0.1 uM

	$C_{31}H_{37}N_3O_5S$ (563.71)	34x @ 10 uM 24x @ 1 uM 2x @ .1 uM 1x @ .01 uM
	$C_{25}H_{26}BrN_3O_5S$ (560.46)	41x @ 10 uM 32x @ 1 uM 3.1 x@ .1 uM 1x @ .01 uM
	$C_{24}H_{24}BrN_3O_5S$ (546.43)	15.5x @ 10 uM 10x @ 1 uM 3.8x @ .1 uM 1.7x @ .01 uM
	$C_{36}H_{34}N_4O_4$ (586.68)	11x @ 10 uM 9x @ 5 uM 5x @ 1 uM 1 x @ 0.1 uM
	$C_{34}H_{30}N_4O_4$ (558.63)	No activity

5.31 Example 31:
Angiotensin II Receptor Binding Assay

[00196] Chinese Hamster Ovary (CHO) cells stably transfected and expressing the human angiotensin II receptor were used for this assay. Cells were cultured to

confluence in DMEM supplemented with 10% fetal bovine serum, 100 mM proline, 1 mg/ml geneticin and antibiotics in wells of a 24 well dish. At the time of assay cells were washed with phosphate buffered saline (PBS) and preincubated for 15 minutes with test compounds (10^{-11} – 10^{-6} M) to allow binding to the receptor. Test compounds were dissolved in DMEM, 0.2% BSA and included potential and verified receptor agonists and antagonists. Following the 15 min preincubation period, cells were incubated with I^{125} –angiotensin for 60 minutes. Following the 60 minute incubation, cells were washed five times with PBS, then dissolved in 1 N NaOH for 15 minutes at 37° C. Aliquots of the solubilized cells were quantitated for radioactive ^{125}I-angiotensin using a gamma counter.

5.32 Example 32:
Measurement of in Vivo Insulin Sensitivity Activity

[00197] Activity of in vivo efficacy of a test compound as an insulin-sensitizing agent is measured as the insulin and glucose-lowering activity of said test compound in the dietary model of insulin resistance. Male Sprague-Dawley rats are placed on a high fat, high carbohydrate diet (Teklad Diet, TD03203 containing 60% fructose, 10% lard, and 0.06% magnesium) at 6 weeks of age. Two days after starting the diet, the rats were randomized into 3 different groups (n = 10 rats per group): Group 1, is treated with the test compound (10 mg/kg body weight per day); Group 2, is the positive control group, telmisartan (10 mg/kg body weight per day); Group 3, is the negative control group (no drug). The compounds were administered by dissolving the commercially available medications in the drinking water at an initial concentration of 40 mg/liter. Food and fluid intakes are measured each day and a pair-feeding protocol is utilized to insure equivalent food intakes among the 3 groups. After 5 weeks, serum levels of glucose, insulin, and triglycerides are obtained in the semi-fasting state (the night before blood draw, animals are given a restricted amount of chow equivalent to 3 grams/100 gram body weight at 5pm and blood and drawn the following morning from the tail vein in the unanesthetized state). The protocol is continued for an additional 9 weeks at which time glucose tolerance testing (OGTT) is performed in conscious animals in the semi-fasted state by sampling blood for glucose and insulin measurements after oral administration of a glucose load (100 mg/100 gram body weight). Serum levels of glucose and triglycerides are measured by spectrophotometric methods and insulin levels were measured by

radioimmunoassay (Linco, St. Louis, MO). Statistical analysis of the data are performed by Student's t test and ANOVA followed by Dunnett's multiple comparison test or the Student-Newman-Keuls test for comparisons across multiple groups. Statistical significance is defined as $P < 0.05$. The insulin-sensitizing activity of the test compounds are calculated as follows:

Insulin-sensitivity activity (%) = {[(PI in C) – (PI in T)]/[PI in C]} x 100

where "PI in C" is plasma insulin in control rats and "PI in T" is plasma insulin in rats treated with test compounds.

5.33 Example 33:

A Clinical Trial Using a dual PPARγ Activator to Treat Type 2 Diabetes Without Causing Fluid Retention, Edema, or Heart Failure

[00198] For the purpose of illustration telmisartan (Micardis®), an angiotensin II type 1 receptor blocker (ARB) which has been shown to activate PPARγ (Benson et al. Hypertension (2004) in press), is used to demonstrate similar clinically beneficial effects anticipated by compounds of this invention which are also dual PPARγ partial agonists and antagonize the angiotensin II type 1 receptor. A 49 year old female with hypertension, hypertriglyceridemia, and type 2 diabetes was selected for therapy. Before administration of telmisartan (Micardis®), the patient had a blood pressure of 147/92 mmHg, fasting serum glucose of 183 mg/dl, a fasting serum triglyceride level of 264 mg/dl, and an HDL cholesterol level of 48 mg/dl. The patient is taking another medication for type 2 diabetes but the dose of this medication is held constant throughout the trial. The patient is given telmisartan at an oral dose of 80 mg/day. After three weeks of telmisartan therapy, the blood pressure is reduced to 143/91 mmHg with little or no improvement in fasting glucose (188 mg/dl), triglyceride (281 mg/dl), or HDL cholesterol levels (50 mg/dl). The oral dose of telmisartan (Micardis®) is then increased to 160 mg/day. After seven weeks of telmisartan (Micardis®) therapy at 160 mg/day, the patient's blood pressure is reduced to 131/81 mmHg and there is a significant improvement in the diabetes with the glucose level reduced to 145 mg/dl, the triglyceride level reduced to 178 mg/dl, and the HDL cholesterol increased to 60 mg/dl. Clinical examination reveals no evidence of any increase in fluid retention, peripheral edema, pulmonary edema, or congestive heart failure. The telmisartan (Micardis®) therapy is continued according to the judgment

of the clinician in order to maintain the improved control of the patient's blood pressure and her type 2 diabetes.

5.34 Example 34:

A Clinical Trial Using a dual ARB/PPARγ Activator to Treat the Metabolic Syndrome Without Causing Fluid Retention, Edema, or Heart Failure

[00199] For the purpose of illustration telmisartan (Micardis®), an angiotensin II type 1 receptor blocker (ARB) which has been shown to activate PPARγ (Benson et al. Hypertension (2004) in press), is used to demonstrate similar clinically beneficial effects anticipated by compounds of this invention which are also dual PPARγ partial agonists and antagonize the angiotensin II type 1 receptor. An obese 52-year-old man (BMI: 34.4 kg/m2, waist circumference: 51 inches) with untreated hypertension, pre-diabetes and the metabolic syndrome was given telmisartan (Micardis®), 80 mg/day, for treatment of high blood pressure. Before administration of telmisartan, the patient had a blood pressure of 160/79 mmHg, fasting serum glucose of 123 mg/dl, fasting insulin level of 30 μU/ml, fasting triglycerides of 136 mg/dl, and waist girth of 120 cm. The patient has the metabolic syndrome as defined by the National Cholesterol Education Program (NCEP). The metabolic syndrome is associated with a 5 - 9 fold increase in the risk for developing type 2 diabetes and a 2 - 3 fold increase risk in cardiovascular mortality. In addition to normalization of his blood pressure, his blood glucose, insulin and triglyceride concentrations also progressively decreased, with an improvement in insulin resistance based on the homeostasis model assessment of insulin resistance (HOMA-IR) score (Table 1). His blood pressure normalized and remained normal throughout the observation period. At week 10, he was switched to a therapeutically equivalent dose of valsartan (Diovan®), an ARB that does not activate PPARγ (Benson et al. Hypertension (2004) in press), at 160 mg/day. After 5 weeks on valsartan (week 15), his glucose, insulin, triglyceride levels, and HOMA-IR score increased, consistent with a reversal in the improved insulin resistance obtained with telmisartan (Table 1). Valsartan was discontinued and he was switched back to telmisartan. Over the following 4 weeks, his insulin resistance and triglycerides again improved (week 19). Clinical examination reveals no evidence of any increase in fluid retention, peripheral edema, pulmonary edema, or congestive heart failure.

[00200] It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of

this disclosure. Accordingly, the present embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope and equivalents of the appended claims.

All publications and patents cited herein are incorporated by reference in their entirety